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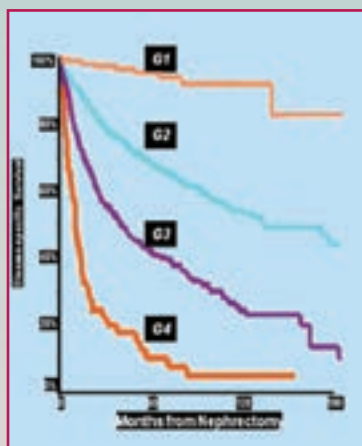
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KIDNEY CANCER

EDITORS

Z. KIRKALI AND P. MULDER



1st EAU-ICUD

International Consultation on Kidney Cancer Barcelona-2010

EAU European
Association
of Urology

Edition 2011

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PREFACE TO ICUD-EAU INTERNATIONAL CONSULTATION ON KIDNEY CANCER 2010



Z. Kirkali



P. Mulders

Kidney cancer remains to be an important item in the agenda of medicine. Better understanding of the mechanisms of renal cancer development, advances in surgery, utilization of alternative therapies and development of effective targeted therapies make kidney cancer a hot topic. The International Consultation on Urological Diseases (ICUD) and European Association of Urology (EAU) with the support of European Organisation for Research and Treatment of Cancer (EORTC) Genitourinary Group organized the 2010 International Consultation on Kidney Cancer. Experts from all around the world gathered in Barcelona during the EAU Annual Meeting on April 16, 2010. Actually this was not a momentous event but a more than a year of planning and hard work of many people. Thanks to the hard work of everyone involved, only 11 months after the event, you are able to hold this excellent book and CD in your hand.

New developments on this disease makes it timely to have a presentation at the and a subsequent consensus report that finally will be presented as a booklet/CD-rom at the 2011 EAU meeting in Vienna.

Usually, when there are many developments in a field during a relatively short period of time, it is not easy to come to a consensus. In this respect, the chairmen of the 7 committees did a tremendous job to set the scene, to create the forum for discussing the relevant evidence and to finalize the elements of the consensus in their respective committees. While the committees went through a consensus process, they followed the Oxford grading system levels of evidence and used the four grades from the Oxford system for recommendations. This was done by a search for papers through the major databases covering the last years as Medline, Pubmed, Embase and Cochrane Library. They searched in relevant journals and evaluated all the papers.

The first committee chaired by Dr.Ljungberg (Umea, Sweden) investigated the ‘*Etiology and epidemiology*’ of renal cell carcinoma (RCC). By describing the risk factors and incidence trends, they obtained the 2010 viewpoint and stated consensus. The second committee was on “Basic research in kidney cancer” and chaired by Dr Oosterwijk from Nijmegen where relevant research results were summarized. The following committee was dealing with “*Pathology*” and chaired by Dr.Algaba from Barcelona, Spain. An extensive description was given on morphology images and cytopathological entities with the latest classification issues described. Committee 4 gave one of the most extensive overviews of “*Prognostic factors*” in renal cell carcinoma. Dr.Karakiewicz (Montreal, Canada) and his committee presented a literature-based overview reaching meta-analysis status. In committee 5, Dr.Van Poppel from Leuven, Belgium and the group gave one of the most detailed overviews of the current literature on “*Treatment of localized RCC*”. With the use of many illustrations it became one of the best publications on this subject so far. “*Treatment of Locally advanced RCC*”: was investigated by committee 6 under the chairmanship of Dr.Wood (Houston, USA). This subject was dealt with in a detailed manner and gave a valuable state-of-the-art on this very timely issue. Finally the “*Treatment of Metastatic disease*” was handled by committee 7 co-chaired by Dr.Bellmunt (Barcelona, Spain) and Dr. Patard (Rennes, France). In a time of rapid changes in the systemic management of RCC, they were able to implement the latest results in their consensus.

The ICUD/EAU 2010 International Consultation on Kidney Cancer is the first-time ever consensus meeting on one of the most hot topics in urologic oncology, Kidney Cancer. The chairmen and the experts in their respective committees have done a wonderful job to produce this state-of-the-art, evidence based knowledge and recommendations. We are grateful to the executive committees of ICUD and EAU respectively represented by Dr.Paul Abrams from Bristol, UK and Dr.Manfred Wirth from Dresden, Germany. Ms.Evelyn White and her team at EAU Central Office were extremely instrumental in logistics. Last but not least, this book could not be realized without the tireless work of Dr.Saad Khoury and his team.

We hope that you will enjoy reading this timely, up-to-date, evidence-based book and find the recommendations of the world-renown experts in kidney cancer useful in your practice.

ZIYA KIRKALI & PETER MULDER
Editors

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CLASSIFICATION OF KIDNEY CANCER

		PRIMARY TUMOR (T)
<input type="checkbox"/>	TX	Primary tumor cannot be assessed
<input type="checkbox"/>	T0	No evidence of primary tumor
<input type="checkbox"/>	T1	Tumor 7 cm or less in greatest dimension, limited to the kidney
<input type="checkbox"/>	T1a	Tumor 4 cm or less in greatest dimension, limited to the kidney
<input type="checkbox"/>	T1b	Tumor more than 4 cm but not more than 7 cm in greatest dimension limited to the kidney
<input type="checkbox"/>	T2	Tumor more than 7 cm in greatest dimension, limited to the kidney
<input type="checkbox"/>	T2a	Tumor more than 7 cm but less than or equal to 10 cm in greatest dimension, limited to the kidney
<input type="checkbox"/>	T2b	Tumor more than 10 cm, limited to the kidney
<input type="checkbox"/>	T3	Tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota's fascia
<input type="checkbox"/>	T3a	Tumor grossly extends into the renal vein or its segmental (muscle containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond Gerota's fascia
<input type="checkbox"/>	T3b	Tumor grossly extends into the vena cava below the diaphragm
<input type="checkbox"/>	T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
<input type="checkbox"/>	T4	Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)
		REGIONAL LYMPH NODES (N)
<input type="checkbox"/>	NX	Regional lymph nodes cannot be assessed
<input type="checkbox"/>	N0	No regional lymph node metastasis
<input type="checkbox"/>	N1	Regional lymph node metastasis
		DISTANT METASTASIS (M)
<input type="checkbox"/>	M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)
<input type="checkbox"/>	M1	Distant metastasis

EVIDENCE – BASED MEDICINE OVERVIEW OF THE MAIN STEPS FOR DEVELOPING AND GRADING GUIDELINE RECOMMENDATIONS.

INTRODUCTION

The International Consultation on Urological Diseases (ICUD) is a non-governmental organization registered with the World Health Organisation (WHO). In the last ten years Consultations have been organised on BPH, Prostate Cancer, Urinary Stone Disease, Nosocomial Infections, Erectile Dysfunction and Urinary Incontinence. These consultations have looked at published evidence and produced recommendations at four levels; highly recommended, recommended, optional and not recommended. This method has been useful but the ICUD believes that there should be more explicit statements of the levels of evidence that generate the subsequent grades of recommendations.

The Agency for Health Care Policy and Research (AHCPR) have used specified evidence levels to justify recommendations for the investigation and treatment of a variety of conditions. The Oxford Centre for Evidence Based Medicine have produced a widely accepted adaptation of the work of AHCPR. (June 5th 2001 <http://minerva.minervation.com/cebm/docs/levels.html>). The ICUD has examined the Oxford guidelines and discussed with the Oxford group their applicability to the Consultations organised by ICUD. It is highly desirable that the recommendations made by the Consultations follow an accepted grading system supported by explicit levels of evidence.

The ICUD proposes that future consultations should use a modified version of the Oxford system which can be directly 'mapped' onto the Oxford system.

1. 1st Step: Define the specific questions or statements that the recommendations are supposed to address.

2. 2nd Step: Analyse and rate (level of evidence) the relevant papers published in the literature.

The analysis of the literature is an important step in preparing recommendations and their guarantee of quality.

2.1 What papers should be included in the analysis?

- Papers published, or accepted for publication in the peer reviewed issues of journals.
- The committee should do its best to search for papers accepted for publication by the peer reviewed journals in the relevant field but not yet published.
- Abstracts published in peer review journals should be identified. If of sufficient interest the author(s) should be asked for full details of methodology and results. The relevant committee members can then 'peer review' the data, and if the data confirms the details in the abstract, then that abstract may be included, with an explanatory footnote. This is a complex issue – it may actually increase publication bias as "uninteresting" abstracts commonly do not progress to full publication.
- Papers published in non peer reviewed supplements will not be included.

An exhaustive list should be obtained through:

- I. the **major databases** covering the last ten years (e.g. Medline, Embase, Cochrane Library, Biosis, Science Citation Index)
- II. the **table of contents** of the major journals of urology and other relevant journals, for the last three months, to take into account the possible delay in the indexation of the published papers in the databases.

It is expected that the highly experienced and expert committee members provide additional assurance that no important study would be missed using this review process.

2.2 How papers are analysed?

Papers published in peer reviewed journals have differing quality and level of evidence.

Each committee will rate the included papers according to levels of evidence (see below).

The level (strength) of evidence provided by an individual study depends on the ability of the study design to minimise the possibility of bias and to maximise attribution.

is influenced by:

• the type of study

The hierarchy of study types are:

- Systematic reviews and meta-analysis of randomised controlled trials
- Randomised controlled trials
- Non-randomised cohort studies
- Case control studies
- Case series
- Expert opinion

• how well the study was designed and carried out

Failure to give due attention to key aspects of study methodology increase the risk of bias or confounding factors, and thus reduces the study's reliability.

The use of **standard check lists** is recommended to insure that all relevant aspects are considered and that a consistent approach is used in the methodological assessment of the evidence.

The objective of the check list is to give a quality rating for individual studies.

• how well the study was reported

The ICUD has adopted the CONSORT statement and its widely accepted check list. The CONSORT statement and the checklist are available at

<http://www.consort-statement.org>

2.3 How papers are rated?

Papers are rated following a «**Level of Evidence scale**».

ICUD has modified the Oxford Center for Evidence-Based Medicine levels of evidence.

The levels of evidence scales vary between types of studies (ie therapy, diagnosis, differential diagnosis/symptom prevalence study).

the Oxford Center for Evidence-Based Medicine Website: <http://minerva.minervation.com/cebm/docs/levels.html>

3. 3rd Step: Synthesis of the evidence

After the selection of the papers and the rating of the level of evidence of each study, the next step is to compile a summary of the individual studies and the overall direction of the evidence in an **Evidence Table**.

4. 4th Step: Considered judgment (integration of individual clinical expertise)

Having completed a rigorous and objective synthesis of the evidence base, the committee must then make a judgement as to the grade of the recommendation on the basis of this evidence. This requires the exercise of judgement based on clinical experience as well as knowledge of the evidence and the methods used to generate it. Evidence based medicine requires the integration of individual clinical expertise with best

available external clinical evidence from systematic research. Without the former, practice quickly becomes tyrannised by evidence, for even excellent external evidence may be inapplicable to, or inappropriate for, an individual patient: without current best evidence, practice quickly becomes out of date. Although it is not practical to lay our “rules” for exercising judgement, guideline development groups are asked to consider the evidence in terms of quantity, quality, and consistency; applicability; generalisability; and clinical impact.

5. 5th Step: Final Grading

The grading of the recommendation is intended to strike an appropriate balance between incorporating the complexity of type and quality of the evidence and maintaining clarity for guideline users.

The recommendations for grading follow the Oxford Centre for Evidence-Based Medicine.

The levels of evidence shown below have again been modified in the light of previous consultations. There are now 4 levels of evidence instead of 5.

The grades of recommendation have not been reduced and a “no recommendation possible” grade has been added.

6. Levels of Evidence and Grades of Recommendation Therapeutic Interventions

All interventions should be judged by the body of evidence for their efficacy, tolerability, safety, clinical effectiveness and cost effectiveness. It is accepted that at present little data exists on cost effectiveness for most interventions.

6.1 Levels of Evidence

Firstly, it should be stated that any level of evidence may be positive (the therapy works) or negative (the therapy doesn't work). A level of evidence is given to each individual study.

- **Level 1** evidence (incorporates Oxford 1a, 1b) usually involves meta-analysis of trials (RCTs) or a good quality randomised controlled trial, or ‘all or none’ studies in which no treatment is not an option, for example in vesicovaginal fistula.
- **Level 2** evidence (incorporates Oxford 2a, 2b and 2c) includes “low” quality RCT (e.g. < 80% follow up) or metaanalysis (with homogeneity) of good quality prospective ‘cohort studies’. These may include a single group when individuals who develop the condition are compared with others from within the original cohort group. There can be parallel cohorts, where those with the condition in the first group are compared with those in the second group.
- **Level 3** evidence (incorporates Oxford 3a, 3b and 4) includes:

good quality retrospective ‘case-control studies’ where a group of patients who have a condition are matched appropriately (e.g. for age, sex etc) with control individuals who do not have the condition.

good quality ‘case series’ where a complete group of patients all, with the same condition/disease/therapeutic intervention, are described, without a comparison control group.

- **Level 4** evidence (incorporates Oxford 4) includes expert opinion where the opinion is based not on evidence but on ‘first principles’ (e.g. physiological or anatomical) or bench research. The Delphi process can be used to give ‘expert opinion’ greater authority. In the Delphi process a series of questions are posed to a panel; the answers are collected into a series of ‘options’; the options are serially ranked; if a 75% agreement is reached then a Delphi consensus statement can be made.

6.2 Grades of Recommendation

The ICUD will use the four grades from the Oxford system. As with levels of evidence the grades of evidence may apply either positively (do the procedure) or negatively (don't do the procedure). Where there is disparity of evidence, for example if there were three well conducted RCT's indicating that Drug A was superior to placebo, but one RCT whose results show no difference, then there has to be an individual judgement as to the grade of recommendation given and the rationale explained.

- **Grade A** recommendation usually depends on consistent level 1 evidence and often means that the recommendation is effectively mandatory and placed within a clinical care pathway. However, there will be occasions where excellent evidence (level 1) does not lead to a Grade A recommendation, for example, if the therapy is prohibitively expensive, dangerous or unethical. Grade A recommendation can follow from Level 2 evidence. However, a Grade A recommendation needs a greater body of evidence if based on anything except Level 1 evidence
- **Grade B** recommendation usually depends on consistent level 2 and or 3 studies, or ‘majority evidence’ from RCT's.
- **Grade C** recommendation usually depends on level 4 studies or ‘majority evidence’ from level 2/3 studies or Delphi processed expert opinion.
- **Grade D** “No recommendation possible” would be used where the evidence is inadequate or conflicting and when expert opinion is delivered without a formal analytical process, such as by Delphi.

7. Levels of Evidence and Grades of Recommendation for Methods of Assessment and Investigation

From initial discussions with the Oxford group it is clear that application of levels of evidence/grades of recommendation for diagnostic techniques is much more complex than for interventions.

The ICUD recommend, that, as a minimum, any test should be subjected to three questions:

1. does the test have good technical performance, for example, do three aliquots of the same urine sample give the same result when subjected to ‘stix’ testing?
2. Does the test have good diagnostic performance, ideally against a “gold standard” measure?
3. Does the test have good therapeutic performance, that is, does the use of the test alter clinical management, does the use of the test improve outcome?

For the third component (therapeutic performance) the same approach can be used as for section 6.

8. Levels of Evidence and Grades of Recommendation for Basic Science and Epidemiology Studies

The proposed ICUD system does not easily fit into these areas of science. Further research needs to be carried out, in order to develop explicit levels of evidence that can lead to recommendations as to the soundness of data in these important aspects of medicine.

CONCLUSION

The ICUD believes that its consultations should follow the ICUD system of levels of evidence and grades of recommendation, where possible. This system can be mapped to the Oxford system.

There are aspects to the ICUD system that require further research and development, particularly diagnostic performance and cost effectiveness, and also factors such as patient preference.

P. Abrams, S Khoury, A. Grant 19/1/04

KIDNEY CANCER

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I. INTRODUCTION

Renal cell carcinoma (RCC) is the most common renal tumour and accounts for approximately 90% of all renal malignancies.[1] Despite advances in diagnosis around 20-30 % of the patients still have metastatic RCC (mRCC) at the time of diagnosis[2]. Around 20–30% of patients undergoing nephrectomy will experience relapse and develop metastasis.[1,3] For these patients with mRCC, outcomes are generally poor and the incidence of RCC and mRCC imposes a serious worldwide epidemiological burden (level of evidence 2)[2]. The general increase in incidence seems to have peaked and decrease in incidence as well as in mortality has been noticed in some countries. Lifestyle factors are the most important etiological factors.

II. INCIDENCE OF RCC

Worldwide, kidney cancer is the 14th most common malignancy with approximately 200,000 new cases diagnosed in 2002.[4] Although RCC is a global problem, the incidence varies geographically [4]. Rates of RCC are high in Europe, North America, and Australia, whereas rates are low in India, Japan, Africa, and China. Until the last years, worldwide incidence has increased by about 2% yearly. (level of evidence: 3).

1. INCIDENCE IN EUROPEAN COUNTRIES:

In 2006, around 64,000 new cases of kidney cancer were estimated in the EU[5,6] (10th most common cancer, **Figure 1**) and 26,400 kidney cancer-related deaths occurred. In the European observatory of cancer of 2009, estimated age-standardized kidney cancer incidence rates per 100,000 Europeans were

14.5 (N=40,395) for males and 6.9 (N=24,656) for females. Czech Republic, Lithuania, Estonia and Iceland have the highest RCC rates in Europe while in Romania, Bulgaria, and Switzerland the incidence was observed lowest [4,6]. Differences in estimated kidney cancer incidence and mortality from kidney cancer among males in 27 European countries, are shown in **table 1**. Although the worldwide incidence of RCC has increased, data from a European study, analyzing kidney cancer incidence between 1980 and 2004, indicate a shift towards stabilization or even a decrease in both sexes in some countries in western and northern Europe, except for England, Scotland and Ireland, whereas incidence in Eastern Europe has increased [7]. (level of evidence: 3). (**Figure 2.**)

2. INCIDENCE WORLDWIDE :

It is estimated that only in the US there will be about 54,000 new cases of kidney cancer and 13,000 kidney cancer-related deaths in 2008.[8] The pattern of occurrence as described for Europe is also observed in the U.S. Data from the Surveillance, Epidemiology, and End Results (SEER) database show a greater incidence increase of RCC diagnosed between 1975 and 1998 for black patients aged 20–59 years compared with white patients of the same age and disease stage (4.5% vs 2.9%, respectively [9,10]. Survival was also lower among black compared with white patients with RCC [6]. A retrospective study of clinical trial populations from 1992 to 2002, supports the finding that race is a predictor of overall survival in patients with mRCC.[11] From the SEER data, it was also observed that Asian Americans had about half the risk of kidney cancer than the other racial/ethnic groups, which is consistent with lower incidence rates of RCC in Asian countries.[9] In Japan also, kidney cancer, is more frequent in males than in females, and shows a substantial geographical difference in total incidence within the country [12,13]

Table 1. Estimated incidence and mortality rates from kidney cancer in men in 27 European countries in 2006; age standardized rate per 100,000 [6].

Country	Incidence	Mortality
Czech Republic	28.9	14.56
Lithuania	27.09	9.95
Estonia	24.26	11.25
Latvia	21.76	10.84
Iceland	20.74	10.19
Poland	20.04	8.73
France	18.8	5.37
Hungary	17.79	7.75
Austria	17.78	5.45
Ireland	17.57	7.02
Belgium	16.47	6.74
Germany	16.43	5.63
Slovakia	15.83	9.03
Slovenia	15.56	7.99
Luxembourg	15.45	9.53
European Union	14.54	5.83
Finland	14.16	6.78
Italy	14.11	4.66
Norway	13.04	5.2
Greece	11.79	4.33
Denmark	10.91	6.42
United Kingdom,	10.84	5.88
The Netherlands	10.83	5.94
Cyprus	10.74	5.66
Malta	10.06	7.52
Sweden	9.92	6.12
Bulgaria	9.69	4.12
Spain	9.29	4.38
Switzerland	8.24	3.6
Portugal	6.9	3.32
Romania	5.73	3.93

III. RCC MORTALITY RATES

Kidney cancer accounted for 102,000 deaths and the rates were about twice as high for males as for females. Overall mortality rates were highest in North America, Australia/New Zealand and Western, Eastern and Northern Europe (Figure 3). Africa and Asia reported the lowest mortality rates [14] (level of evidence: 1).

In 2006 in the European Union the estimated number of kidney cancer death was 27,326, around 2.2 % of all cancer deaths (16,798 males (rate 5.8) and 10,528 females (rate 2.6). The overall mortality rates

for kidney cancer in EU countries have increased until the late 1980s/early 1990s, thereafter rates have stabilized or declined.[7] (Figure 2.) In total the mortality rates declined from 4.8 per 100,000 in 1990–1994 to 4.1 in 2000–2004 in men, and declined from 2.1 to 1.8 per 100,000 in women.[4] (level of evidence: 3). The changing mortality rates in the EU vary among the different countries. In Scandinavia, a decrease in mortality is observed since the 80s, whereas a decrease since the early 1990s is seen in France, Germany, Italy, Austria, and The Netherlands. The decreases were generally greater in men than in women. Some European countries do not show decreased mortality rates and an increased rate has been observed in some of the eastern European countries [7]. This favorable trend in mortality within the EU, might in part be accounted for by improvements in diagnosis and treatment, and by the rising incidence of small renal masses, but it can not be fully explained.[15,16] (level of evidence: 3).

In the US, overall mortality rates of patients with kidney cancer have increased from 1.5 per 100,000 in 1983 to 6.5 per 100,000 in 2002.[17] This increase might be at least partly be explained by the fact that small tumors are more successfully treated and 5-year relative survival rates have improved over time for patients with RCC from 56.4% (diagnosed 1983–1987) to 68.9% (diagnosed 1998–2002). [16] After the beginning of 2000s the rates have been leveling off and slightly declined until 2006, a similar trend as is present in Europe where the rates have been declining in most countries.[7,18,19] (level of evidence: 3).

RECOMMENDATIONS: None

IV. ETIOLOGICAL FACTORS

1. SEX:

Age-standardized incidence rates of RCC have generally been reported to be higher among men than women [1]. This pattern is consistently observed throughout the world with the exception of Western Africa where reported incidence rates seemed to be higher among women. Incidence data, in particular from more developed regions of the world, suggest that men are at an increased risk of developing RCC (level of evidence: 3).

2. RACE:

Reported age-standardized incidence rates of RCC are highest in Europe and Northern America [1]. The incidence rates seem to be substantially lower among Asians both in most Asian countries and in the US [1-3]. These observations suggest a higher risk of RCC among whites compared to Asians (level of evidence: 3). The lowest incidence rates have been reported from African countries [1], but on

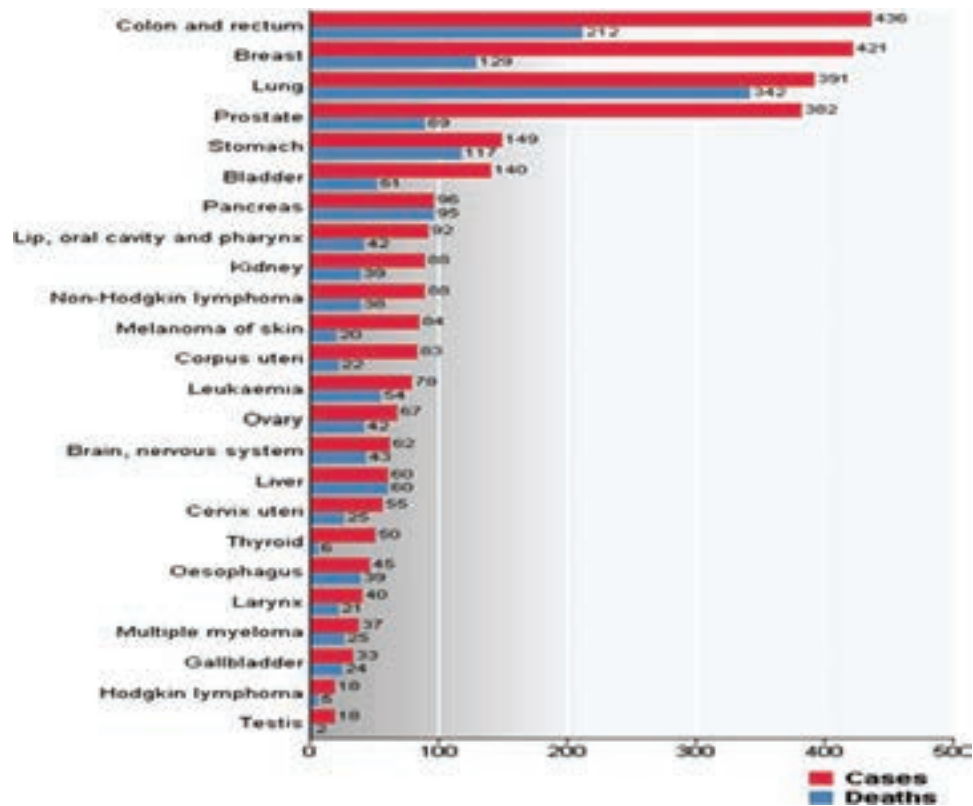


Figure 1. Estimated number of cancer cases and deaths in 40 European countries 2008. Based on an illustration in Farley J et al, *EUROPEAN JOURNAL OF CANCER* 2010; 46, 765–781.

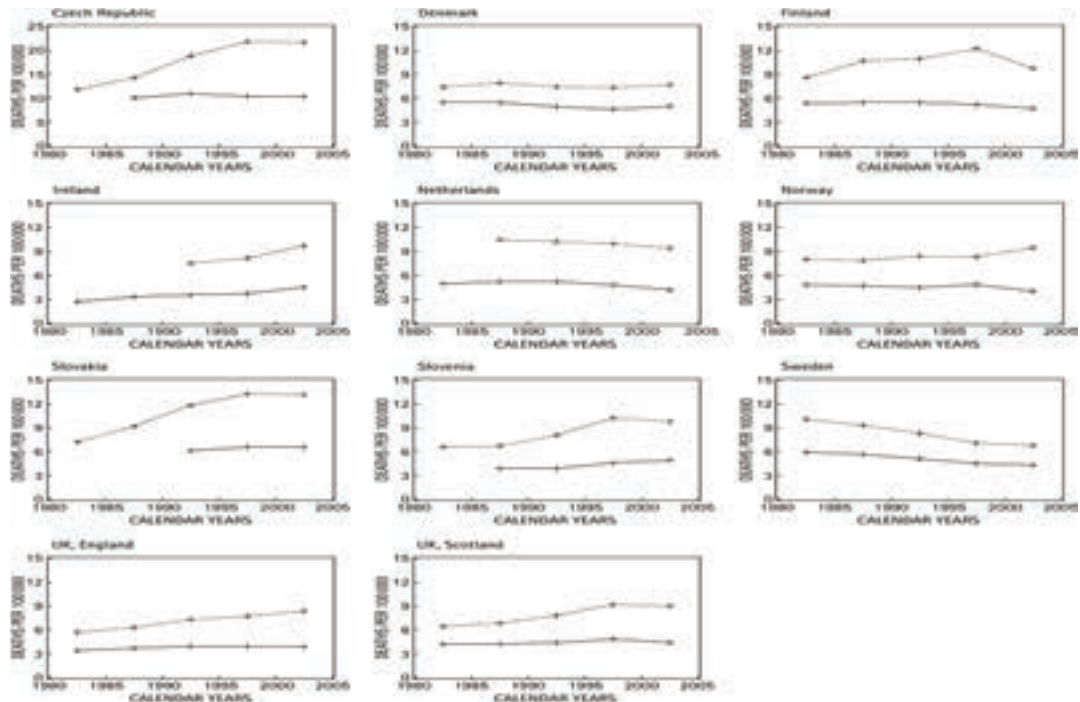


Figure 2. Trends in overall age-adjusted incidence and mortality from RCC per 100 000 men in 11 European countries between 1980 and 2004. From Levi F, et al. *BJU Int.* 2008;101(8):949-58.

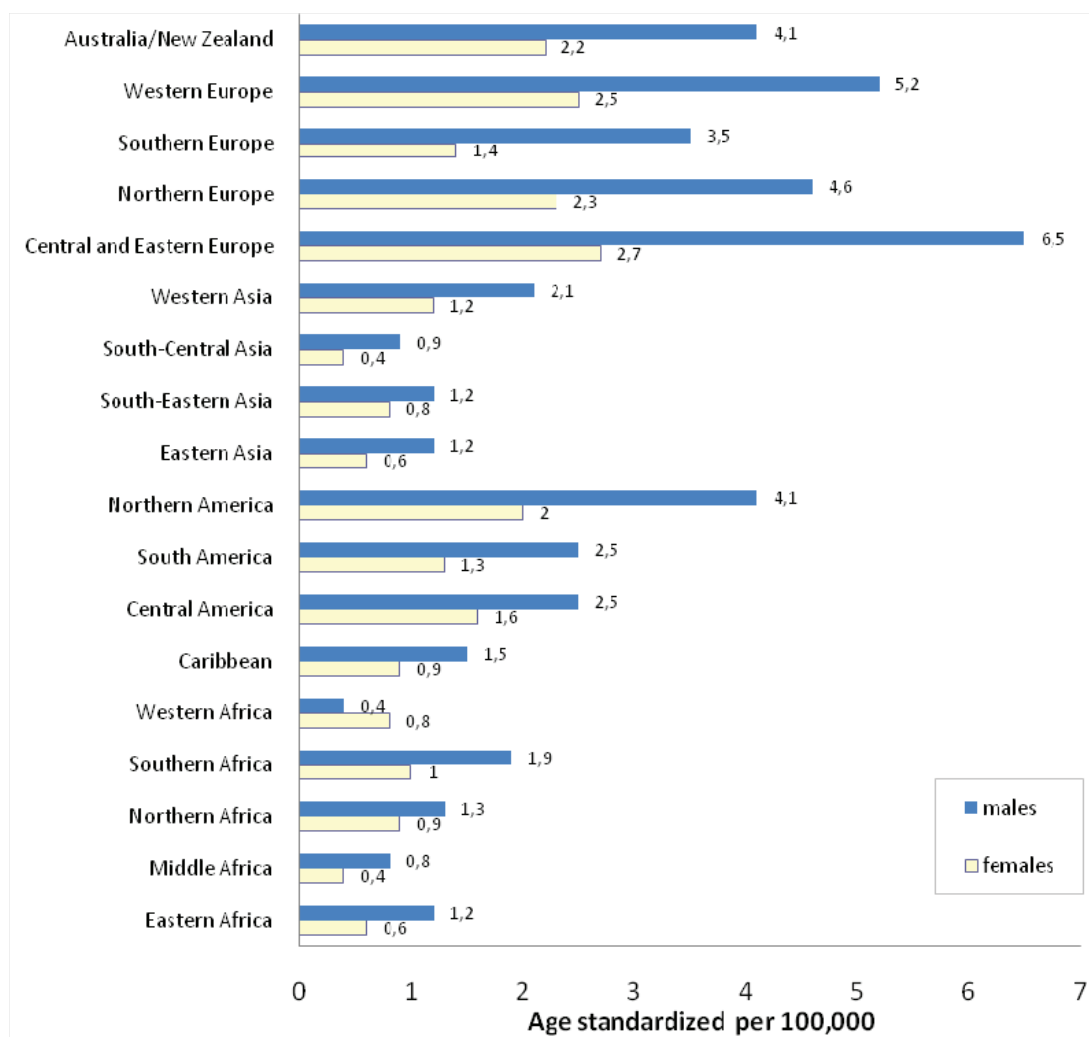


Figure 3. Age-standardized mortality rates for kidney cancer by gender in different continents (Global Cancer Statistics, 2002 [14])

the contrary the incidence rates are highest among African Americans in the US [2, 3]. Racial disparities in incidence rates may be attributable to differences in frequency of diagnostic imaging, access to health care, and prevalence of other risk factors. At present, evidence on an independent association between race and RCC risk is inconclusive.

3. AGE:

Data from the “Cancer Incidence in Five Continents” database at IARC and the U.S. the Surveillance, Epidemiology, and End Results (SEER) program indicate that incidence rates in Europe and USA increase consistently with age, with a plateau reached around the age group of 70-75 years and above [2, 4]. The latter effect may be due to less frequent diagnostic testing in this age group.

4. CIGARETTE SMOKING:

Cigarette smoking has been established as a risk factor for RCC by a large number of studies. A meta-analysis [5] including 19 case-control and 5 cohort studies confirmed that ever smoking increases the risk of RCC compared to never smoking (level of evidence: 2). The increases in risk related to ever smoking were estimated to be 54% for men and 22% for women. The association between smoking and RCC is relatively weak but a clear dose-response relationship is evident with higher risk estimates with heavier smoking [5] (level of evidence: 2).

There is only limited evidence to suggest that smoking cessation may reduce the risk of RCC in ever smoking men after 10 years or longer of non-smoking [5-7] (level of evidence: 3). Limited data

from few case-control studies suggest a potential association between passive smoking and RCC [7-9] (level of evidence: 3).

5. OVERWEIGHT/OBESITY:

Excess body weight has been established as a risk factor for RCC in several case-control and cohort studies. Most studies investigated body mass index (BMI) using self-reported body weight and height. A meta-analysis [10] of prospective studies provided evidence for an association between BMI and risk of RCC with summary risk estimates (per 5 kg/m² increase in BMI) of 1.24 in men and 1.34 in women (level of evidence: 2). The results suggested a somewhat stronger association in women than in men, but this difference was not robust and mainly driven by one large Norwegian cohort study [11]. A quantitative review of earlier studies found equally strong associations among men and women. Overall, evidence on sex-specific differences in the association between BMI and RCC risk is not conclusive. Studies investigating body fat distribution suggested an increased risk of RCC with increasing waist-to-hip ratio [12-15] (level of evidence: 3), but evidence is too limited to conclude that abdominal obesity is a risk factor of RCC independently of BMI. Limited data suggest an increased risk of RCC with weight gain or weight fluctuations [12, 13, 16] (level of evidence: 3).

6. BLOOD PRESSURE, HYPERTENSION AND USE OF ANTIHYPERTENSIVE MEDICATIONS:

Hypertension or its treatment has been associated with the risk of RCC in several prospective cohort studies [14,16-24] (level of evidence: 2). Three cohort [16, 23, 24] and one case-control study [25] measured blood pressure and observed an increased risk of RCC with elevated blood pressure, with a clear dose-response relationship reported in two cohort studies [16, 24] (level of evidence: 2). Two other prospective cohort studies observed an increased risk of RCC mortality with elevated blood pressure in men (Figure 4. 26, 27). The independent contribution of blood pressure level and antihypertensive medication use have generally been difficult to distinguish, as most studies are based on a diagnosis of hypertension that is inevitably linked to treatment with antihypertensive drugs. Data from one case-control study and one adequately powered cohort study indicate that high blood pressure, rather than the use of antihypertensive medication increases RCC risk [24, 25] (level of evidence: 3). Other studies did not consider blood pressure and medication use independently of each other. Data from two cohort studies suggest that better control of blood pressure may lower RCC risk [16, 24] (level of evidence: 3), whereas use of antihypertensive medications including diuretics is probably not a causal risk factor [17, 19, 24, 25] (level of evidence:

3). The association observed between use of diuretics and other antihypertensive drugs may thus be due to confounding by a history of hypertension, but data on this issue remain inconclusive.

7. CONCLUSIONS:

Cigarette smoking, excess body weight according to increases in BMI, and hypertension are the most prevalent modifiable risk factors of RCC increasing the risk independently of each other in both sexes.

Long-term smoking cessation may reduce RCC risk in men, while its influence in women is unclear.

Body fat distribution may impact RCC risk independently of BMI, but further studies are necessary.

Elevated blood pressure increases RCC risk while use of antihypertensive medications per se may not be a risk factor as long as blood pressure is effectively controlled.

8. RECOMMENDATIONS:

Reductions in the prevalence of cigarette smoking, excess body weight, and uncontrolled blood pressure are recommended as preventive strategies for RCC (Grade B recommendation). Smoking cessation can possibly decrease RCC risk in ex smokers after 10 years or longer (Grade C recommendation). Effective control of blood pressure may decrease RCC risk in individuals with hypertension (Grade C recommendation).

V. GENETIC FACTORS

1. FAMILIAL AND HEREDITARY RENAL CANCER SYNDROMES

Overall, approximately 2-3% of RCC are familial, i.e. primarily due to inherited genetic defects (See table 2) [47,48]. Each of the common histologic subtypes of RCC has a corresponding familial syndrome, and each of these is caused by a distinct genetic alteration [49]. All of these syndromes are relatively rare, such as VHL which appears to be the most common, although found in only 1/36,000 births. These syndromes should be considered in patients with early onset and/or multifocal/bilateral disease. Some are due to mutated or inactivated tumor suppressor genes and others to activated oncogenes, but all are transmitted in an autosomal dominant manner. Genetic counseling and gene sequencing should be considered, and appropriate screening for the other manifestations of the syndromes should be performed [50]. Family members at risk should also be counseled to consider relevant clinical and genetic testing. Most of these syndromes can be managed conservatively at least until tumor size

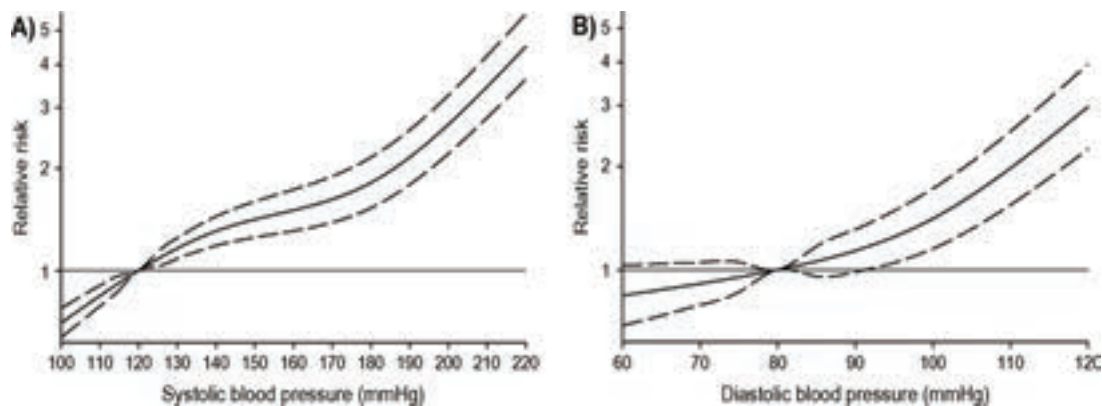


Figure 4. Relative risk functions of RCC according to systolic (A) and diastolic (B) blood pressure in a population based prospective cohort study (EPIC). From Weikert et al, *Am J Epidemiol* 2007.

reaches 3.0 cm, because the risk of metastasis remains relatively low until this threshold is reached. Nephron-sparing approaches are preferred in an effort to delay or preclude the need for dialysis [51]. One exceptional syndrome is familial leiomyomatosis RCC in which the tumors are often highly aggressive – a more proactive approach is often indicated in this syndrome.

2. VHL SYNDROME

The familial syndrome for clear cell RCC is VHL in which patients can also develop hemangioblastomas of the central nervous system, retinal angiomas, and pheochromocytomas. Benign tumors in the inner ear, pancreas, and epididymis are also common [52]. Penetrance for each of these manifestations is far from complete, e.g. RCC is only found in about 40-50% of patients. The VHL gene is located at 3p25-26 and produces a protein that normally targets hypoxia-inducible factors (HIFs) for ubiquitin-mediated degradation. Loss of function leads to accumulation of HIFs and subsequent upregulation of VEGF and other factors that promote angiogenesis and tumor growth [53]. Tumors in this syndrome thus tend to be highly vascular contributing to their potential morbidity. Nephron-sparing approaches are preferred but VHL kidney tumors can be lethal, and RCC is the most common cause of death in this syndrome [50].

RECOMMENDATION: Active screening for RCC in patients with this syndrome can allow for early detection and improved clinical outcomes. (Grade C recommendation)

3. HEREDITARY PAPILLARY RCC

Hereditary papillary RCC is caused by activation of the c-met proto-oncogene on chromosome 7q31, which encodes a growth factor receptor. Mutations

lead to constitutive activation of the receptor, which promotes tumor growth. Type 1 papillary RCC is exclusively observed in this syndrome, which is unique in that it does not present with manifestations in other organ syndromes [48].

4. FAMILIAL LEIOMYOMATOSIS RCC

Familial leiomyomatosis RCC can present with cutaneous leiomyomas and women often have a history of hysterectomy for uterine leiomyomas at an early age. Type II papillary RCC with a tendency towards aggressive tumor biology is characteristic [48, 53]. The fumarate hydratase gene on chromosome 1q42 has been correlated with this syndrome, although research to link this Krebs cycle enzyme to malignant transformation is still in progress.

5. BIRT-HOGG-DUBÉ SYNDROME

Birt-Hogg-Dubé (BHD) syndrome, in which patients develop cutaneous fibrofolliculomas, lung cysts, spontaneous pneumothoraces, and a variety of renal tumors primarily derived from the distal nephron, is the final familial RCC syndrome characterized as of 2010. Renal tumors typically include chromophobe RCC, oncocytomas, and hybrid or transitional tumors that exhibit features of both of these entities [49]. However, other forms of RCC, including clear cell RCC, have also been observed in this syndrome, which is unique in the diversity of tumor types that have been reported. Overall penetrance for renal tumors is about 20-40%. Most renal tumors in BHD have limited biological aggressiveness, although metastatic behavior and lethality have been reported. This syndrome has been correlated to mutations in the folliculin tumor suppressor gene on chromosome 17p11.2 [50].

Table 2. Familial Renal Cell Carcinoma Syndromes. [49,52] Adapted from Campbell SC, Lane BR: Malignant Renal Tumors. Campbell-Walsh Urology, 10th edition. Edited by Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA, Elsevier, Philadelphia, PA, Chapter 49, in press, August, 2009.

Syndrome	Genetic Element	Major Clinical Manifestations
Von Hippel-Lindau	VHL gene (chromosome 3p25-26)	Clear cell RCC Hemangioblastomas of the central nervous system Retinal angiomas Pheochromocytoma
Hereditary papillary RCC	c-met proto-oncogene (chromosome 7q31)	Type 1 papillary RCC
Familial leiomyomatosis and RCC	Fumarate hydratase (chromosome 1q42)	Type 2 papillary RCC Cutaneous leiomyomas Uterine leiomyomas
Birt-Hogg-Dubé	Folliculin (chromosome 17p11.2)	Chromophobe RCC Oncocytoma Transitional tumors* Occasional clear cell RCC Cutaneous fibrofolliculomas Lung cysts Spontaneous pneumothorax

**Also known as hybrid oncocytic tumors and containing features of both chromophobe RCC and oncocytoma.*

Adapted from Campbell SC, Lane BR: Malignant Renal Tumors. Campbell-Walsh Urology, 10th edition. Edited by Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA, Elsevier, Philadelphia, PA, Chapter 49, in press, August, 2009.

VI. ETIOLOGY OF OTHER DISEASES

1. ACQUIRED RENAL CYSTIC DISEASE

Acquired renal cystic disease (ARCD) consists of multiple hyperplastic renal cysts on each kidney. It happens in patients with end stage renal disease (ESRD) and most often seen in patients on long-term hemodialysis.[54-56] ARCD is also frequently associated with adenomas and can progress to RCC.[57]

The incidence of RCC in ARCD is much higher than general population. Studies in the US reported a

three to six time higher incidence.[58,59] In Japan, RCC develops several to twenty times higher in dialysis patients than in the general population.[60] Therefore ARCD is a definite high risk factor of RCC. (level of evidence: 2b). Also an association of RCC with a period of dialysis was investigated. The study reported that patients who had 10 years of dialysis developed no signs of RCC even 15 years forwards.

It is controversial that renal hyperplastic cysts and adenomas undergo malignant transformation. Bretan [62] et al insisted that there might be a progression from benign renal cyst to epithelial hyperplasia and to RCC based on the findings of renal tumors occurring in hyperplastic epithelium of some complicated cysts. But no other studies validated the theory.

RCC occurring in ESRD has a few characteristics different from classic RCC. The age when RCC is diagnosed is younger in patients with ESRD than in the general population. The incidence ratio of male to female is higher in patients with ESRD than in the general population. (7:1 vs 2:1, respectively) [63]

Some investigators reported that the cysts in the patients with ARCD reduce after renal transplantation.[64] However, the risk of RCC after renal transplantation may not decrease. Levin[65] et al. and Heine[66] et al. reported RCC developing after transplantation.

2. DIABETES

Diabetes mellitus (DM) is known to be associated with an increased risk of several cancers. However, DM is a controversial risk factor in RCC.[67-71] Two cohort studies reported significantly increased risk of RCC in patients with DM with relative risk of 1.3 in men and 1.7 in women,[68,69] but most of other studies failed to prove a relation between DM and risk of RCC.[71-73] Two international renal-cell-cancer studies observed borderline or no direct association.[70,74]

A recent epidemiologic study did not find significant ORs between DM and RCC. The authors concluded that overweight and obesity are weakly associated with RCC but attributing DM as a risk factor is controversial.[75] (level of evidence: 3)

3. URINARY TRACT INFECTION

Cohort studies regarding UTI history as an independent risk factor for RCC are limited. Chow et al.[76] investigated the incidence and risk of UTI in a population-based cohort of 61,144 patients hospitalized for urinary stones in Sweden from 1965 to 1983. After 25 years of follow-up, Chow et al. reported on no increase in the incidence of RCC for the subset of cohort patients who had a history of UTI.

In 5 case control studies McLaughlin et al.[77], Hiatt et al.[78], and Parker et al.[79] reported an increased risk of RCC associated with a history of UTI while Schlehofer et al.[80] and McCredie et al.[81] reported no association. These conflicting results indicate that UTI is not an independent risk factor for RCC. (level of evidence: 3)

4. CONCLUSIONS:

ARCD is definitely a risk factor of RCC and patients with ESRD should be regularly screened. It is unclear whether transplantation reduces the risk of RCC. Diabetes and urinary tract infection are controversial as independent risk factors of RCC.

5. RECOMMENDATIONS:

In ARCD, regular screening of the kidney (Grade B recommendation) is recommended for early diagnosis for RCC.

VII. NUTRITIONAL FACTORS, DIET AND RENAL CELL CANCER (RCC)

There is more than a 10-fold difference in incidence of kidney cancer between high-income countries and middle/low-income countries [82]. Incidence has increased more than 90% in less than 20 years in Eastern Asia [83,84], coinciding with dramatic changes in food supply and dietary patterns. Together these data suggest that lifestyle, including diet, plays a role in RCC development.

1. NUTRIENTS

a) Protein and Fat

An ecologic study has reported that the per capita daily intakes of fat and protein are positively correlated with the incidence of kidney cancer in both men and women [85] (level of evidence: 3).

High protein consumption has been hypothesized to increase RCC risk because of the potential unfavorable effect on the kidney of nitrogen waste products. Most case-control studies have reported non-significant or significant positive associations between intakes of total or animal protein and the risk of RCC [86-88] (level of evidence: 3). However, prospective studies, which avoid selection and recall bias because participants start to be followed from the beginning of the study, and dietary information is collected prior to diagnosis of RCC, have been less supportive. A pooled analysis of 13 prospective cohort studies in the US, Canada, and Europe [89] and a large European collaborative study [90] observed no association between total, animal, or plant protein and RCC risk (level of evidence: 2).

Results of case-control studies on total fat or various types of fat intake (vegetable, animal, dairy, saturated, monounsaturated, polyunsaturated, trans fat, and cholesterol) and RCC risk have been inconsistent [87,88,90-92], and no association was found in a collaborative analysis of 13 prospective cohort studies [89] (level of evidence: 2).

b) Vitamins

Prospective studies of multivitamin use and risk of RCC have found no association [93,94] (level of evidence: 2). Other supplemental use or intake of vitamins (from both foods and supplements), including folate and vitamins A, C, D, and E, have not shown consistent results [87,93,95-101]. One recent large case-control study that examined

genetic polymorphisms of vitamin D receptor genes suggested that vitamin D could play a role in RCC [102] (level of evidence: 3), but this possibility needs further study.

c) Other nutrients

Among studies that have examined associations between RCC and nutrients abundant in fruits and vegetables, such as dietary fiber [87,90,91], individual carotenoids [87,88,95,98,101,103], and flavonoids [97,104,105], many case-control studies and a pooled analysis of cohort studies found an inverse association for some of these nutrients [95,103,106,107] (level of evidence: 2). However, this may be partly explained by the inverse association for intake of fruits and vegetables noted in the same populations [95,103,106,107]. Because studies on total carbohydrate [87,90,91] or minerals [87,96,107] are sparse, their findings cannot be considered conclusive.

2. FOOD GROUPS

a) Fruits and vegetables

Although the results for fruits and vegetables from case-control studies of RCC have been inconsistent [86,87,106-110], the largest such studies (each with more than 500 RCC cases) have shown more consistent inverse associations for total fruit [87], total vegetables [87,106,109], and subgroups of vegetables [87,95,107,109] (level of evidence: 3).

In a prospective study, a pooled analysis of 13 cohort studies found that fruit and vegetable consumption was associated with a lower risk of RCC [22] (level of evidence: 2) whereas studies of a large European [111] and a US [112] cohort did not find an inverse association (level of evidence: 2).

b) Meat and Fish

The consumption of red or processed meat was associated with increased risk of RCC in a meta-analysis of case-control studies [113] and in other case-control studies [109,110,114] (level of evidence: 2). However, a pooled analysis of cohort studies found no increase in risk for either red meat or processed meat [89] (level of evidence: 2). The data on poultry intake were not consistent [89,109,110].

Total fish intake was not associated with RCC risk in case-control studies [109,114] or in a pooled analysis of 13 cohort studies [89] (level of evidence: 2). Although one Swedish cohort study suggested a lower risk of RCC among women with high fatty fish consumption [115] (level of evidence: 2), studies on specific type of fish consumption are few.

c) Alcohol, coffee, and other beverages

The main functions of the kidney are to regulate water and inorganic-ion balance and to excrete

waste products and foreign chemicals [116]. Because complicated chemical exchanges take place in renal tissues, the risk of RCC may be affected by the quantity and type of beverages consumed.

Studies on intake of alcohol or alcoholic beverage showed suggestive increase or no associations [87,88,95,117]. However, recent case-control [118-120] and cohort studies [121-123] showed that moderate alcohol consumption was significantly inversely associated with risk of RCC (level of evidence: 2). Total fluid intake was not associated with RCC risk [124] (level of evidence: 2), suggesting that the duration that carcinogenic solutes are in contact with RCC may be unrelated to the mechanism by which alcohol prevents RCC risk.

Coffee intake was not associated with RCC risk in most case-control studies [88,92,95,125,126], but a pooled analysis of cohort studies found a lower risk of RCC with coffee consumption [127] (level of evidence: 2).

Findings on other beverages including soft drinks, juice, milk and tea were inconsistent in prospective studies [127,128] and in case-control studies [86-88,106,109,110,117,125,129,130].

3. OTHER FOOD GROUPS

Results were inconsistent for cereals, grain products, glycemic index, glycemic load [87,88,107,110,131-133], and dairy products other than milk including eggs, yogurt, ice cream, cheese [87,88,97,106,107,109].

VIII. OCCUPATION

Worldwide, kidney cancer occurs about twice as frequent among males as among females. Because of this male/female ratio and the widespread interest in health effects related to occupational exposures, several studies investigated associations between occupation and kidney cancer.

Quite a few studies presented clearly increased risk of kidney cancer related to several occupations, possibly because of historical high exposure levels. A large international case-control study found significant associations with employment in the blast-furnace or the coke-oven industry (RR 1.7), the iron and steel industry (RR 1.6) and exposure to asbestos (RR 1.4), cadmium (RR 2.0), dry cleaning solvents (RR 1.4), gasoline (RR 1.6) and other petroleum products (RR 1.6) (level of evidence: 3). [134] Similar associations were found in a multicenter study from Germany. [135] These studies were conducted in the nineties with questionnaires about exposures in the decades before that. Nowadays, in general, strongly increased risks are not found anymore, although a recent study conducted in Central and Eastern

Europe, the area with the highest rates of kidney cancer worldwide, suggested an association between kidney cancer and agricultural work particularly among female workers (level of evidence: 3).[136]

A commonly reported toxic mineral with suggested nephrocarcinogenicity is asbestos.[1] A more recent meta-analysis of asbestos-exposed cohort studies concluded, however, that there is unconvincing evidence of an increased association, although high asbestos exposure might cause a small increase in risk (level of evidence: 2).[137]

Workers exposed to high levels of polycyclic aromatic hydrocarbons, like coke and coal oven workers, were reported to have an increased risk of kidney cancer (level of evidence: 3).[134-1] The results of two cohort studies showed a highly significant excess of mortality among steelworkers as coke oven workers, but after a follow-up of 30 years no increased mortality risk was found anymore (level of evidence: 2).[138] Also, a study of European asphalt workers did not show an increased kidney cancer risk [139]

Findings indicate that there is no association between oil refinery workers, who are highly exposed to gasoline, and risk of kidney cancer. A population-based case-control study of occupational exposure conducted in the 1980s in Canada found an OR of 1.0 for both gasoline and other exposure to lead and kidney cancer.[140] The same was true in a study from Sweden where occupational diesel exposure was not found to be related to kidney cancer (level of evidence: 3).[141]

Perchloroethylene is a primary solvent in the dry cleaning industry which may be carcinogenic to humans.[142] A review of occupational exposure to perchloroethylene and cancer did not support this suggestion and reported that apart from limitations and inconsistencies in the published literature, a relationship between PCE and kidney cancer is unlikely (level of evidence: 3).[143] Trichloroethylene (TCE), a solvent used as a poor degreaser for the cleaning of metal parts, was linked to kidney cancer because of evidence of carcinogenicity in experimental animals, and some regions in Germany have a high TCE exposure[144] But these findings are not supported by the results of other investigations that concluded that the carcinogenicity of trichloroethylene in humans remains a matter of controversy (level of evidence: 3).[145]

Recently a case-control study of pesticides exposure and kidney cancer showed a significantly increased risk[146], but more studies are needed to confirm these findings (level of evidence: 3).

CONCLUSION: Based on the literature, overall, kidney cancer is not considered to be a typical occupation-related tumor.[147]

RECOMMENDATION: It is generally recommended to decrease or prevent exposure to occupational carcinogens (e.g., asbestos, polycyclic aromatic hydrocarbons, dry cleaning solvents, cadmium) by means of modifications of production processes or protective interventions. Such policies may also lower the risk of renal cell cancer, but presumably to a small extent only (Grade C Recommendation).

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Basic Research in Kidney Cancer

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Basic Research in Kidney Cancer

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I. INTRODUCTION

Cancer of the kidney is expected to affect almost 100,000 patients in the United States and European Union in 2010 [1;2]. Renal cell carcinomas (RCC) refer to cortically derived tumors of the renal parenchyma and encompass a heterogeneous group of cancers [3]. Advances in basic research aimed at defining pivotal molecular events in the development of these different entities has shown that renal cancers can be subdivided based on genetic profiles. Moreover, knowledge of underlying molecular characteristics identified the vascular endothelial growth factor (VEGF) and the mammalian target of rapamycin (mTOR) pathways as fundamental to the biology of clear cell RCC. This biologic insight provided a rationale for targeting these growth factor signaling pathways in RCC.

Basic science in RCC is a vast area therefore we will focus on four areas of research that were felt most relevant for renal cancer and are not discussed in-depth in other chapters: the molecular basis of renal cancer, targeted therapies, renal cancer and immunity, and genetic factors and RCC. Finally, it is important to note that great majority of basic research in RCC is focused on clear cell RCC given the high prevalence of this histological subtype. Additionally, while the vast majority of studies have been performed on material from primary lesions, future studies should consider examination of metastatic lesions as well.

II. THE MOLECULAR BASIS OF RENAL CANCER

Historically, four main histological renal cancers were recognized in the Heidelberg classification: clear

cell Renal Cell Cancer (ccRCC, 60-80%), papillary RCC (10-15%), chromophobe RCC (~5%) and renal oncocytoma (~5%) [3;4]. Recently, translocation linked [5;6], mucinous tubular and spindle type RCC [7] and tubulocystic carcinoma [8] (all comprising <1% of cases) have been added to this list. It is now clear that these morphological subtypes represent highly dissimilar diseases in both genetics and clinical behavior, and thus may or may not be variants of a common cancer or common cell of origin (Figure 1).

The biology of the von Hippel-Lindau (VHL) gene product, pVHL, and its regulation of the hypoxia inducible factor (HIF) family of hypoxia-regulated transcription factors, is tightly linked to ccRCC biology. The discovery of the VHL gene, and its association with the VHL syndrome of central nervous system hemangioblastomas, pheochromocytoma/paraganglioma, and ccRCC, in 1993 [9] quickly led to the discovery that VHL mutation is also tightly associated with sporadic ccRCC, detected in up to 90% of tumors [10-13]. The loss of VHL leads to the loss of regulation of HIF family members HIF1 α , HIF2 α [14-18], and HIF3 α [19], which is further composed of several splice variants. Xenograft studies have demonstrated that restoration of pVHL expression or suppression of deregulated HIF2 α impairs the growth of these tumors [20;21].

Papillary RCC, chromophobe RCC and renal oncocytoma are less dominated by mutations in a single gene. Mutations in c-met have been associated with familial papillary type 1 RCC, but only in a subset of sporadic papillary RCC, and is thus less dominant than VHL is for ccRCC [22]. A more rare, but also highly aggressive type of papillary type II renal cell carcinoma has been associated with mutations in the fumarate hydratase gene [23], although the relevance of this mutation in sporadic disease is unknown. Heterogeneous knock out of the gene

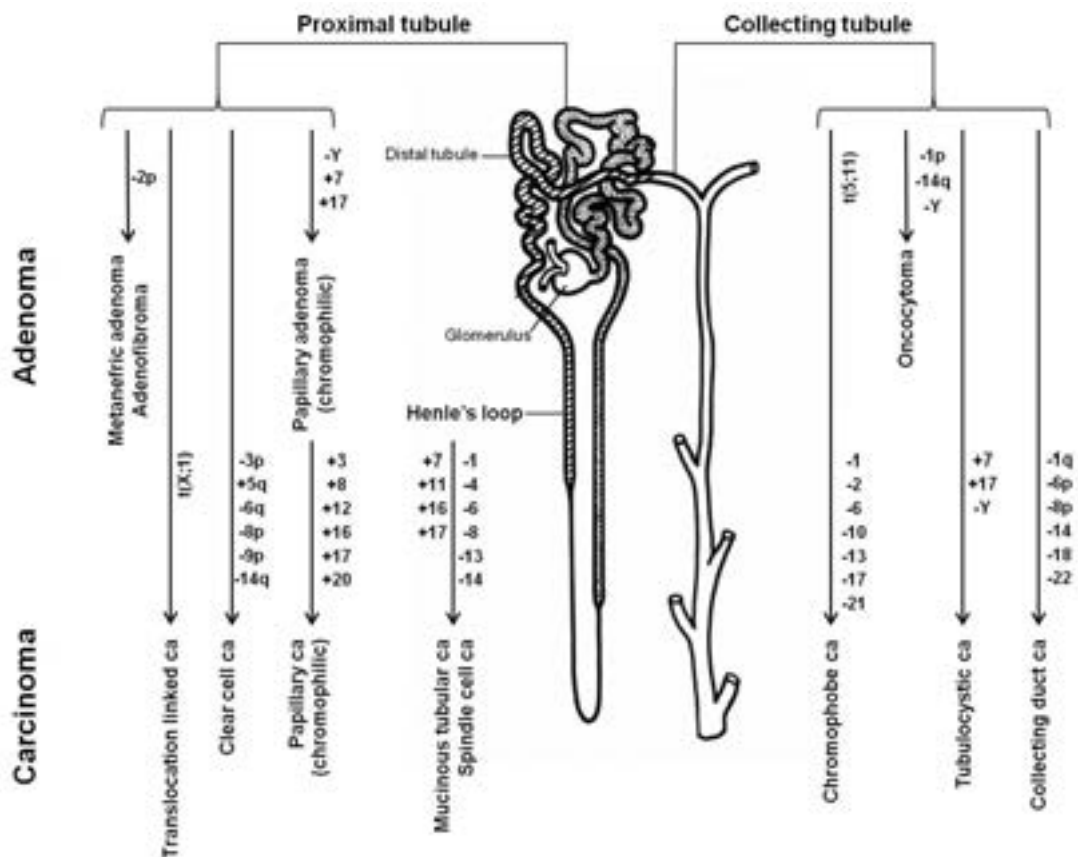


Figure 1: Schematic representation of the nephron and the different subtypes of RCC according to the 'Heidelberg' classification in relation to their positions within the nephron and collecting tubule. Genetic changes that are characteristic for the different RCC subtypes are indicated.

implicated in the Birt-Higg-Dubé (BHD) syndrome in mice leads to the development of renal cysts and three different histological types of renal tumors, similar to human BHD which is closely associated with familial chromophobe RCC, but predisposes to other histologies as well [24].

In spite of the tight correlation of ccRCC with inactivation of VHL, the effect on HIF deregulation is not uniform: a variant mutations in VHL may contribute to imbalances of HIF1 α and HIF2 α deregulation, leading to distinct effects on cell growth [25;26]. In a strategy to determine whether tumors could be defined based upon the most studied and understood pathway in RCC, gene expression profiles were linked with VHL mutation analysis and expression characteristics of the HIFs [27]. In this study, 160 ccRCCs were classified as VHL mutant or wild type and according to HIF protein expression. VHL mutant, HIF1 and HIF2 expressing tumors (H1H2) overexpressed the Akt/mTOR pathway, while VHL mutant tumors expressing solely HIF2 (H2 tumors) replicated more rapidly, marked by overexpression of Ki-67, which other groups have identified as a poor-

risk marker [28]. ccRCC can thus be characterized as H1H2 or H2, with dramatically differing effects on tumor cell proliferation and C-myc regulation [27]. Recent evidence suggests that the H2 tumors may be derived from H1H2 tumors that lose HIF1 α in a subset of tumors, suggesting a potentially selective pressure to lose the HIF1 α gene during tumor progression [29]. These insights potentially narrow the key tumorigenic events within the VHL/HIF axis.

Besides VHL loss and HIF activation, major efforts have tried to identify a simple linear progression of genetic lesions accounting for the gains in aggressiveness in RCC [30-34]. Two recent ccRCC cytogenetic studies lend clues to understanding this progression. One study performed both single nucleotide polymorphism (SNP) analysis and gene expression analysis on sporadic ccRCC and tumors from patients with VHL disease [30]. Importantly, this study demonstrated that tumors from sporadic and VHL-disease ccRCC tumors have overall similar profiles, but sporadic tumors are more heterogeneous and contain a higher number of genetic events per tumor, but they cannot be

distinguished using unsupervised analysis of gene expression data. In a prospective analysis of 282 ccRCC patients with up to 108 months of follow-up using traditional cytogenetic karyotyping techniques [32] chromosomal loss at 3p (the genomic home of the VHL gene) was significantly associated with improved disease-specific survival, while losses of 4p, 9p and 14q were significantly associated with reduced disease-specific survival, but the specific genes in these regions implicated in causing the poor prognosis remain to be characterized.

The first whole sequencing study in ccRCC confirmed that considerable genetic heterogeneity exists in ccRCC [29] emphasizing that even though the vast majority of ccRCC contain mutated VHL most likely every tumor has a unique gene signature. This study also substantiated findings in multiple mouse knock-out studies and a zebrafish study which demonstrated that VHL mutations/knock out alone is insufficient to produce ccRCC and that additional genetic events are required [35;36].

Although unable to cause sporadic ccRCC alone, the presence and type of VHL mutations in tumors have been consistently considered as possible biomarkers. Cowey, et al, recently reviewed its potential in prognosis and prediction [37]. Further research is still required to establish VHL's efficacy as a biomarker, but given the frequency of its inactivation, more opportunities to understand the heterogeneity of this disease may lie in exploration of downstream factors. When VHL is inactivated and HIF expression constitutively stabilized, a host of other genes which make up various components of the hypoxia response are transcriptionally upregulated (reviewed in [38]). It remains to be determined which of these factors or pathways most significantly contributes to the formation or maintenance of ccRCC's malignant phenotype. One HIF target, the vascular endothelial growth factor (VEGF), has been found to be significantly upregulated in kidney tumors compared to its elevated expression in many other cancers. As a prognostic biomarker, VEGF has not been proven to be valuable, but may be predictive of response to VEGF targeted therapy, as described below.

In order to identify more effective biomarkers and further understand the underlying biology, several different groups performed gene expression analyses on ccRCC tumor samples. **Table 1** gives an overview of these studies. One of the initial expression profiling studies examined 29 ccRCC tumors, identifying 51 genes that could classify tumors based on 5 year disease-specific survival [39]. This study verified the possibility that gene expression profiles could be used to predict outcome in ccRCC, but remains to be validated or defined by biological parameters that may account for this difference in disease activity. One study of 51 tumor samples identified vascular cell adhesion molecule-1, VCAM-1, as a prognostic

biomarker [40], which has subsequently undergone retrospective validation [41;42]. Importantly, high expression of this molecule predicted for better overall survival in both clear cell and papillary tumors, suggesting that VCAM-1 expression may generally indicate tumor cells with lower metastatic potential. The further implications for sensitivity to antiangiogenic therapy are not yet known.

Several gene signatures for RCC progression, for example three genes (caveolin 1, lysyl oxidase, and annexin A4) have been identified as associated with RCC aggression and/or survival [43] [44]. Similarly, survival was shown to independently predict clear cell progression and risk of death [45] [46]. Finally, the largest study, analyzing 177 clear cell tumors, identified 340 transcripts (including VCAM-1) significant in multivariate analysis with stage, grade and performance status [47] [48].

While the above studies focused on clinical endpoints in their analyses, many started with an unsupervised analysis to get a general understanding of the data. The study that identified VCAM-1 as a prognostic biomarker saw the presence of potentially two subgroups within the stage IV tumors, with survival differences [40]. This suggests that molecular features beyond clinical staging could provide informative data in understanding even metastatic tumor behavior. The group of Zhao, et al. examined their 177 tumors using 3,674 genes also observed two larger groups of ccRCC, with significant survival differences as well as predicted biological pathway distinctions [47]. These studies helped to set the stage for further delineation of subgroups within ccRCC.

Two other studies stand out as being predominantly geared toward identifying the inherent subgroups and underlying biological differences of ccRCC. One group first looked at 16 ccRCC tumors and saw that there seemed to be two types of clear cell, one that more highly overexpressed metabolic genes and the other extracellular matrix/cell adhesion genes [49]. Most recently, a bioinformatic technique called unsupervised consensus clustering was used on 48 tumors to identify two subtypes of ccRCC, ccA and ccB, distinguished by fewer than 120 probes [50]. Validating these results in the Zhao, et al., data set of 177 tumors, patients with ccA tumors have a markedly survival advantage over those with ccB tumors. Additionally, this dataset validates the characteristics that ccA tumors display a profile of altered metabolism, whereas ccB tumors display characteristics of wound healing and epithelial to mesenchymal transition.

Finally, one study focused entirely on metastases [51], finding that late occurring metastases more highly expressed genes involved in angiogenesis, cell migration and adhesion. Additionally, genes

Table 1: Gene expression studies in RCC (reproduced with kind permission from Springer Science+Business Media: Curr Oncol Rep: Renal cell carcinoma: where will the state-of-the-art lead us? Volume 12 (2010) 193-201, Brannon AR, Rathmell WK, [116]).

Study	Year	Samples	Analytical focus	Results
Clinically driven analyses Takahashi [39]	2001	29 clear cell 29 normal	5 year survival	51 probes associate with survival, 96% accuracy
	2003	51 clear cell 6 papillary 1 unknown	Survival	45 genes most associated with survival. VCAM-1 alone can stratify patients by survival.
	2005	22 clear cell 10 metastases 37 other 24 normal	Progression and metastases	31 genes that are continuously deregulated in disease progression. 155 genes that associate with metastases, 88.9% accuracy
	2005	10 aggressive cc 9 non-aggressive cc 9 metastatic cc 12 normal	Tumor aggressiveness	35 genes distinguish between non-aggressive and aggressive tumors. Survivin expression associated with survival by multivariate analysis in 183 patients
Zhao [47]	2006	177 clear cell	Unsupervised	2 primary clusters composed of 5 subclusters with survival difference.
Yao [119]	2008	25 clear cell (14 metastatic) 2 metastases	Metastatic vs non-metastatic	3 genes (VCAM-1, EDNRB, RGS5) that by qRT-PCR associate with survival
Wuttig[51]	2009	20 metastatic clear cell	Disease-free interval Number of metastases	306 differentially expressed genes differentiate early (≤ 9 months) versus late (≥ 5 years) occurring metastases 163 probe sets differentiate patients with multiple (≥ 16) and “few” (≤ 8) metastases
Biology-driven analyses Vasselli [40]	2003	51 clear cell 6 papillary 1 unknown	Unsupervised	2 clusters of metastatic tumors with survival difference
	2006	16 clear cell 21 normal	Unsupervised	2 subtypes distinguishable by 546 genes, with possible pathway differences
Zhao [47]	2006	177 clear cell	Survival	259 genes associated with survival by univariate and multivariate analysis
Gordan [27]	2008	21 clear cell	Wild-type VHL vs H1H2 vs H2 tumors	3 groups have distinct biological pathways. H2 tumors overexpress c-Myc, leading to increased proliferation

Table 1: Gene expression studies in RCC (reproduced with kind permission from Springer Science+Business Media: Curr Oncol Rep: Renal cell carcinoma: where will the state-of-the-art lead us? Volume 12 (2010) 193-201, Brannon AR, Rathmell WK, [116]). (Continued)

Study	Year	Samples	Analytical focus	Results
Zhao [48]	2009	177 clear cell	Biology of survival gene set	Good prognosis tumors resemble normal renal cortex or glomerulus. Poor prognosis tumors associated with wound healing and loss of differentiation gene sets.
Brannon [50]	2010	48 clear cell 18 normal	Unsupervised consensus clustering	2 subtypes of clear cell (ccA and ccB) with pathway and survival differences, differentiable by <120 probes
Gene Expression and CytoGenetics/Sequencing Analyses				
Furge [31]	2004	60 clear cell 5 papillary 16 chromophobe	Histological classification by virtual cytogenetics	1018 gene classifier and cytogenetic classifier to distinguish between 3 subtypes, 99% and 81% accuracy, respectively.
Sultmann [34]	2005	65 clear cell 13 papillary 9 chromophobe 25 normal	Cytogenetics; Metastases and survival	136 genes significantly associated with cytogenetic abnormalities. 45 genes associated with survival. 85 genes associated with metastasis formation.
Beroukhim [30]	2009	49 sporadic cc 5 metastases 36 VHL tumors	VHL disease vs sporadic clear cell	VHL disease and sporadic clear cell tumors have similar gene expression and cytogenetic profiles, but sporadic cases have more frequent alterations.
Dalglish [29]	2010	96 clear cell	Genetics by sequencing	Mutations in histone modification and DNA damage repair genes may be important in RCC development or progression

cc, Clear Cell; H1H2, HIF-1 and HIF-2 overexpressing; H2, HIF-2 only overexpressing; VHL, von Hippel Lindau

related to cell division and cell cycle were overexpressed in samples from patients with multiple metastases, indicating that the presence of more metastases might be caused by an increased growth potential.

All of the potential biomarkers emerging from the gene expression studies require removal and processing of at least part of the tumor. Plasma serum proteins have traditionally been studied to find non-invasive diagnostic markers for the presence of ccRCC as compared to normal or benign renal tissue. Currently, there are no circulating tumor markers available for clinical use in management of RCC. Several molecules have been studied as candidates for diagnosis of RCC: In clear cell RCC the results with VEGF and VEGFR have been contradictory [52;53], and these markers might be more suitable as predictive than as diagnostic markers. Recent studies have shown elevated CAIX levels in ccRCC patients [54], with a significant association between CAIX serum levels and occurrence of metastases [55]. Furthermore, in patients with localized disease an elevated CAIX level predicts the recurrence and is correlated with a shorter PFS. Again, there is not a complete concordance with tissue results. Other markers related to tumor biology like MMP-7, CD95, bFGF, hepcidin-25, IL-10 or IL-6 showed promising results as possible biomarkers for RCC [56-60], but these markers need to be validated in separate studies.

Because of the complexity of the tumor development and progression, identification of complex protein signatures is more promising. High throughput technologies like MALDI (Matrix assisted laser desorption/ionization) or SELDI (Surface Enhanced Laser Desorption/Ionisation) allow the analysis of the whole proteome of many samples in a short time with high sensitivity. SELDI-TOF-MS (Time of Flight Mass Spectrometry) has especially been used to define prognosis related profiles. Unique protein signatures of tumor patients compared to normal controls with high sensitivity (70-87%) and specificity (89.9-92%) have been described [56-63]. One of the candidate proteins, SAA1, was identified by 3 groups [61;64;65]. In all published studies, elevated SAA1 concentration correlated with metastasis, poor prognosis and shorter survival [61;64-66], even though different cut-off values were used. Independent studies are needed to substantiate the value of SAA1.

Finally, an 831 tumor tissue microarray study analyzed 15 proteins that are associated with the pVHL and phosphatase and tensin homologue (PTEN) pathways [67]. Surprisingly, while pVHL and phospho-mTOR staining correlated inversely with tumor stage and grade, neither protein correlated with survival. Within the intermediate stage tumors (pT2 and pT3), tumors with p27 and CAIX expression associated with improved outcome. This study suggests that

the dysregulation of several independent pathways are crucial for tumor progression, corroborating the sequencing study by Dalglisch, et al. [29].

MicroRNA, 21-23 nucleotide segments of single-stranded non-coding RNA, have now been implicated in tumorigenesis of many cancers, even being identified as potential prognostic biomarkers in several of these (reviewed in [68]). The aberrant expression of these non-coding RNAs can provide a powerful method of epigenetic tumor regulation, as an individual microRNA can alter the expression of many target genes. In RCC, various studies have identified various individual or panels of microRNAs that are differentially expressed between normal renal tissue and tumor or between histological subtypes [69-76]. The identification of relevant targets of these tumor associated microRNAs are just becoming realized [74]. MicroRNAs can be easily extracted from formalin fixation, paraffin embedded tissue, and blood. The ability to easily use non-invasive measures to identify a stable target makes microRNAs a very attractive biomarker for diagnostic, prognostic, and predictive purposes.

A large number of potential biomarkers have emerged from all these gene expression studies. Encouragingly, trends are beginning to emerge between studies. The next important step will be bringing these potential biomarkers and biomarker profiles to the clinical arena.

III. TARGETED THERAPIES IN RCC

The increased understanding of the fundamental disease biology of RCC has been translated into the development of therapies with inhibitory activity against the implicated pathways, particularly the VEGF and mTOR pathways. A number of tyrosine kinase inhibitors (TKI) have now been registered for treatment of metastatic RCC (mRCC) (sunitinib, sorafenib, pazopanib) and more TKI (e.g. axitinib, tivozanib) are being developed. The rapid and simultaneous emergence of several active compounds has far outpaced the ability to critically understand precise mechanisms of response and resistance [77] (Figure 2).

Surprisingly, the TKI were clinically implemented with very few preceding pre-clinical studies. For example, the cross-reactivity of TKI with non-target (non-VEGF-receptor) TK [78] was established after clinical implementation and preclinical studies in various animal models demonstrated stabilization or regression of non-grafted tumors (mostly in non-RCC models). The rationale to study this new category of drugs in RCC patients was based on theoretical considerations that these TKI attack pathways essential in RCC biology and, therefore, might be appropriate new drugs for RCC therapy.

Indeed, the effects of TKI in RCC patients are impressive, with objective response rates as high as 45% (reviewed by e.g., Rini et al. [79]), but treatment is often accompanied by many side effects requiring dose reduction or cessation of treatment.

TKI treatment of RCC patients leads to a massive destruction of the tumor vasculature with concomitant tumor necrosis. Whether RCC cells themselves are targeted remains uncertain [80]. At pharmacological relevant doses no effect on tumor cells was observed [80] and there is evidence that tumor co-option occurs, i.e., tumor growth along larger mature vessels, permitting tumors to escape TKI treatment. Additionally, resistance to existing VEGF blocking agents may include upregulation of HIF- and/or non-

HIF-mediated angiogenic proteins or inadequate target inhibition. mTOR therapy resistance may involve a compensatory increase in upstream elements leading to HIF production [77].

Obviously, predictive biomarkers for response to TKI in mRCC patients are urgently needed, and some have been described. Serum from patients with clinical response or progression was screened by cytokine arrays to discover that TNF-alpha and MMP-9 levels remained low in responders [81]. Additionally, high levels of these proteins in the serum correlated with decreased overall survival. In another study, low serum levels of sVEGFR-3 and VEGF-C corresponded with longer progression free survival (PFS) and objective response rate in bevacizumab-

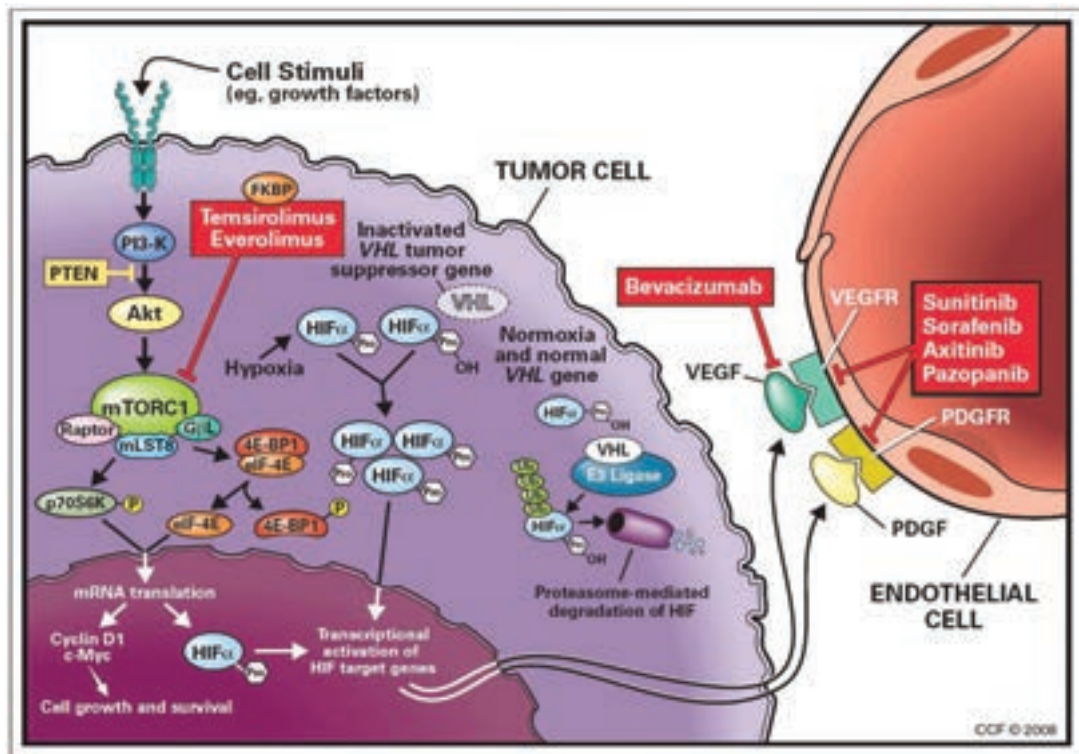


Figure 2: In conditions of normoxia and normal von Hippel Lindau (VHL) gene function, VHL protein is the substrate recognition component of an E3 ubiquitin ligase complex that targets hypoxia-inducible factor alpha (HIFα) for proteolysis. In cellular hypoxia or with an inactivated VHL gene, the VHL protein-HIF interaction is disrupted, leading to stabilization/accumulation of HIF transcription factors. HIF accumulation can also result from activation of mammalian target of rapamycin (mTOR) downstream of cellular stimuli and the PI3-K/Akt pathway. mTOR phosphorylates and activates p70S6K leading to enhanced translation of certain proteins including HIF. Activated HIF translocates into the nucleus and leads to transcription of a large repertoire of hypoxia-inducible genes including vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF). These ligands bind to their cognate receptors present on the surface of endothelial cells, leading to cell migration, proliferation and permeability. Sites of action of targeted therapies are illustrated. Temsirolimus and everolimus bind to FK506-binding protein (FKBP), and the resultant protein–drug complex inhibits the kinase activity of the mTOR complex 1 (mTORC1). Bevacizumab is a VEGF ligand-binding antibody. Sunitinib, sorafenib, axitinib and pazopanib are small molecule inhibitors of multiple tyrosine kinase receptors including VEGF-R and PDGFR (Reprinted with permission. © 2008 American Society of Clinical Oncology. Rini BI: Metastatic renal cell carcinoma: many treatment options, one patient. J Clin Oncol 2009;27:3225-34.)

refractory mRCC [82]. A third study suggested that large changes in serum VEGF, sVEGFR-2 and sVEGFR-3 levels corresponded with tumor response [83], and a fourth study found a correlation between fold-increase of serum VEGF and clinical benefit [84]. All of these potential predictive biomarkers require external validation in larger sample sizes, but suggest that serum may prove to contain cogent markers of survival and response.

IV. RCC AND THE IMMUNE SYSTEM

There is increasing evidence that TKI treatment leads to alterations of the immune status of RCC patients [85;86]. Sunitinib can reverse myeloid-derived suppressor cell induced immune suppression, but other studies indicate that Sunitinib can inhibit the proliferation of primary human T cells from normal healthy volunteers as well as from RCC patients [87]. Moreover, sunitinib treatment appears to reverse Th1 suppression and impairs NK function. Similarly, sorafenib treatment impairs NK activity and cytotoxicity at pharmacological levels [85]. Also, sorafenib treatment leads to a decrease of Treg in primary lesions and Treg levels decrease to normal levels after sorafenib treatment. Whether the immune component is important and might be used to our advantage in designing combination therapies is an uncharted field [86].

It is important to realize that RCC tumors develop in immune competent hosts and that these tumors have escaped from immune surveillance and immune editing leading to tumor cells that are resistant to immune-system mediated destruction (Figure 3) [88]. Nevertheless, to date, immunotherapy is the only treatment that can consistently induce durable complete clinical responses in mRCC [89].

Several studies have demonstrated the ability of tumor infiltrating lymphocytes (TIL) to induce tumor response in mRCC with objective response rates between 0 and 25 %, with concomitant infusion of IL-2 [90-95]. At UCLA, patients with largely advanced and metastatic disease received a combination of TIL/CD8+ and IL-2. Overall, 9.1 % of patients achieved CR while 25.5% had a PR showing the potential of TIL in mRCC [94]. Taken together these studies demonstrated the need of using highly selective and specific activation methods of effector cells in order to achieve a meaningful antitumor immune response. Unlike melanoma, where specific T-cell clones against well-defined tumor epitopes can be frequently generated, T-cell clones that specifically recognize kidney cancer tumor antigens are hard to generate. The proof of concept of isolating these clones and successfully treat patients with mRCC has however been well established. On the other

hand, given the in vitro work needed to isolate TIL, this approach still needs to prove that it induces better clinical responses than HD-IL2 alone.

Side studies of clinical trials with dendritic cells loaded with cell lysates, peptides, or RNA or Treg depletion have demonstrated the induction of specific T cell responses, but no clear correlation between clinical benefit and the occurrence of a immune reaction was found [96;97]. There is evidence that various factors hamper an anti-tumor response: defective CD8 signaling, a Th2-bias, and elevated levels of gangliosides from T cells are associated with T cell dysfunction[98;99]. Basic research aimed at understanding the relation between RCC and immune cells have revealed an increasingly complex picture with many players. Cross-talk between RCC and dendritic cells (DC), Treg, CD4+, CD8+, NK-cells, $\gamma\delta$ T cells, NK-like T cells, and Myeloid Derived Suppressor Cells, have been described[100]. The plasticity of cells from the immune system is extraordinary and the tumor milieu plays a pivotal role and can greatly influence the outcome.

In recent studies, efforts were poised at gene-modified T-cells [101] and multimodality immune-based strategies [102]. Gene-modified T cells in melanoma has shown interesting results with two CR [103]. For RCC, infusion of gene-modified T cells with CAIX specificity lead to liver toxicity, probably due to destruction of bile epithelial cells that also express CAIX [101]. Although this demonstrated that the gene-modified did exert the desired specificity, the observed toxicity also highlights the potential problems of this approach: extraordinary tumor specificity appears to be of utmost importance. In the multi-modality immune-based strategy the CA9 and GMCSF genes were inserted in an adenovirus genome to infect DC which allowed the expression of the GMCSF/CA9 fusion protein [102]. Overexpression of the fusion protein in DC through adenoviral infection CA9 specific T cells could be generated with toxicity against RCC. Hence, this new strategy combines many immunotherapy approaches: 1) the immunostimulatory effects of cytokines; 2) the adjuvant capabilities of DC and; 3) the specific antitumor activity generated by tumor antigen gene delivery in APC. Indeed, the CA9-GMCSF/DC based vaccine is an example of the new multimodality immune-based strategies that may enhance the well-established potentials of immunotherapy in RCC.

The effectiveness of tumor vaccines has been shown in many animal models. However, translation to the clinic has proven difficult, possibly because in these model systems naturally occurring tumors have not been studied, thereby avoiding tumor surveillance and tumor editing. Thus, the concept is tested in immune competent hosts that are vaccinated with peptides or tumor homogenates and challenged with viable

tumor cells or, alternatively, vaccination strategies are tested in animals with established tumors. Initial tumor vaccines were based on total tumor cell lysates that were injected to the patients (autologous tumor cell vaccines). However, new strategies using genetically modified tumor cells, antigen presenting cells (APC) or tumor specific peptides have been developed to increase the specificity of the response. Two phase-III clinical trials that have used autologous cell lysate or peptides to prevent recurrence in high-risk RCC patients have been published [104;105]. Jocham et al. have reported a statistically significant increase in 5-year PFS (77.4 vs 67.8%, $p=0.0204$) for the vaccine group in high-risk non-metastatic RCC patients. More recently, Wood et al. published a similar study in high-risk non-metastatic patients using heat shock protein derived peptide vaccines and did not observe a statistical difference in PFS ($p=0.51$). However, secondary analysis did show an almost statistically significant PFS survival when only stage I and II patients were included ($p=0.056$).

Therefore, vaccine approaches show great promise in preventing recurrence after nephrectomy but the subgroups of patients that would benefit from such therapy still need to be determined. Animal models in which the natural history of human RCC can be replicated will be of great value to test this concept more rigorously.

V. GENETIC FACTORS AND RCC

Epidemiological studies have conclusively identified three risk factors for the development of RCC: hypertension, obesity and smoking [106-108]. Furthermore, there is evidence that genetic factors influence susceptibility to RCC; for instance, the life-time risk increases approximately two-fold for those with a first-degree relative with RCC [109]. Thus far, candidate gene studies have not yielded notable candidate genes. In a recent genome-wide association study (GWAS) of RCC three susceptibility

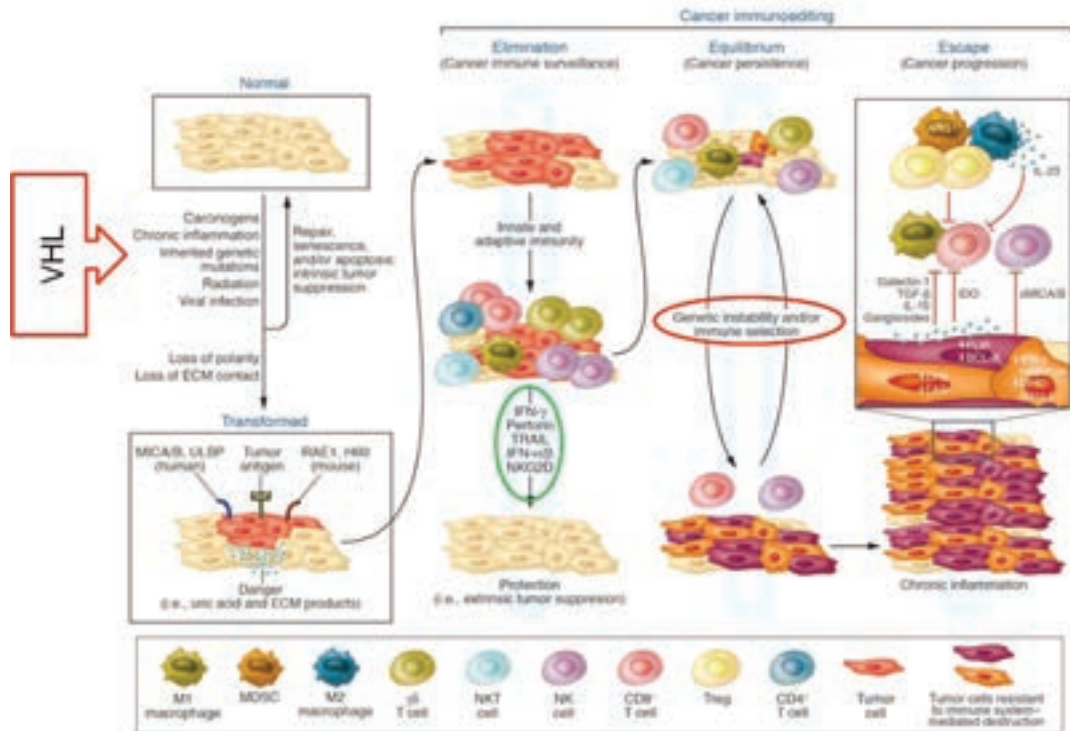


Figure 3: Extrinsic tumor suppression by the immune system. Transformed cells (in this example kidney cells with mutated VHL) escaping intrinsic control are subjected to extrinsic tumor suppressor mechanisms that detect and eliminate developing tumors before they become clinically apparent. This is known as the elimination phase of a broader process that has been termed cancer immunoediting. Cancer immunoediting is now considered a process composed of 3 phases: elimination, or cancer immune surveillance; equilibrium, a phase of tumor dormancy where tumor cells and immunity enter into a dynamic equilibrium that keeps tumor expansion in check; and escape, where tumor cells emerge that either display reduced immunogenicities or engage a large number of possible immunosuppressive mechanisms to attenuate antitumor immune responses leading to the appearance of progressively growing tumors (Figure adapted from Swann JB, Smyth MJ. Immune surveillance of tumors. *J Clin Invest* 2007;117:1137-46. Reprinted with permission).

loci on chromosomes 2p21 (EPAS1), 11q13.3 and 12q24.31 (SCARB1) were identified (Purdue et al, submitted). The findings from the GWAS provided further evidence that EPAS1 (HIF2 α) is a key gene in RCC development, but additional studies are needed to identify the functionally relevant common variants associated with increased risk.

Up to now little attention has been paid to inter-ethnic variability or individual differences, whereas this is an important aspect in the current TKI era. Patients of afro-american descent have higher incidence rates and lower survival rates compared to all other races, also when diagnosed with localized disease. In contrast, Asian/Pacific Islander patients have lower incidence rates and higher survival rates than all the other ethnicities [110]. Furthermore, response to treatment and frequency of severe toxicity is related to ethnic origin, most likely due to different pharmacokinetics and not the genetic nature of the disease. Sunitinib, sorafenib and pazopanib have been associated with significant toxicity profiles which vary widely. Higher toxicities during cytotoxic chemotherapy have been reported in patients enrolled Japanese trials compared to patients in American or European trials [111]. Ethnic differences in hematological toxicity have been attributed to the varying activities of drug –metabolizing enzymes and transporters that are mainly associated with polymorphisms in the promoter and coding regions of these enzymes [111]. In a phase II study assessing the efficacy and safety of sunitinib in Japanese patients, the incidence of hematological adverse events was numerically higher than those previously reported in western trials, however the AUC values for sunitinib were similar in both groups [112].

In the only pharmacogenetic study published until now, 31 single nucleotide polymorphisms in 12 candidate genes, together with several non-genetic variants, were analyzed for a possible association with toxicity [113]. Encouragingly, particular haplotypes (most notably by polymorphisms in CYP1A1) could be correlated to sunitinib-related toxicity. Because race-related differences in the frequency distribution of four genetic polymorphisms in the CYP1A1 P450 enzyme genes have been identified between Japanese and Caucasian populations, this may partly explain the inter-ethnic differences observed [114].

VI. CONCLUSIONS

In the last decade, great strides have been made in the understanding of molecular mechanisms underlying renal cell carcinoma patients. The state-of-the-art has clearly led this field to the enviable position of having a range of molecularly targeted therapies. Nevertheless, despite the clear improvement in the therapeutic options for mRCC patients, therapies targeting the tumor cells themselves are highly desirable. Better models,

closer resembling the natural course of renal cancer are needed. It is foreseen that through integration of various high-throughput platforms personalized cancer treatment for renal cell carcinoma patients is possible. There are further improvements expected on the horizon: recent effort have made progress toward using formalin-fixed paraffin-embedded tissues for molecular analyses (including DNA and RNA recovery), which will permit studies on enormous archives of existing specimens [115] including metastatic lesions, a hitherto understudied area; mature profiles of protein and nucleic acid biomarkers will help us to define the spectrum of tumors that lie under the umbrella of ccRCC; and a future unmapped territory of genetic mutations to explore that may provide more tools and answers to the questions we ask. There is great hope for the future of renal cell carcinoma treatment, and it will be exciting to see what new advances will be made in the decade to come.

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Pathology

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Pathology

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I. HISTORICAL BACKGROUND

The microscopic characterisation of Renal Cell Carcinoma (RCC) started in the mid-19th century with the controversy aroused by Grawitz's hypothesis. In 1883 Grawitz stated that "alveolar" (clear cell) tumours, previously considered lipomas, were originated in the neoplastic transformation of adrenal cortical residues into renal cortical. One year later he confirmed his theory when he found ectopic adrenal cortex in the renal cortex [1]. This theory was readily opposed by Sudek who considered the renal tubular origin [2]. The controversy between supporters and detractors of the Grawitz theory went on for decades. The term *Hyponephroma* was introduced in 1909, and made reference to its adrenal origin [3]. Even though the support to the supposedly adrenal origin started to grow weaker, and finally Oberling et al.'s ultrastructural studies [4] put a full stop to the argument when they demonstrated the tubular origin of renal carcinoma.

At this moment the international classifications unified all histological types under the common denomination of renal adenocarcinoma; this could be a clear cell or a granular cell carcinoma, its architecture could be tubular, papillary or cystic, and its appearance was rarely sarcomatoid [5].

One of the major advances was Thoenes et al.'s description of the *chromophobe renal cell carcinoma* [6], morphologically different from the clear cell carcinoma and probably originated in the intercalated cells of the distal nephron [7]. From this description (initially not accepted by the international classifications), the possibility of determining different origins of the histological subtypes started to be searched with monoclonal antibodies [8]; unfortunately, for the overlapping of the markers it

was not possible to differentiate groups, so no kind of modification of the established classification was finally determined.

It was only when Koopman's initial chromosome studies [9], subsequently redefined by the Heidelberg classification [10], were introduced that the renal cancer microscopic subtypes were taken into account again, as a correspondence was confirmed between genetic abnormalities and microscopic phenotype.

II. FROM THE CLASSICAL TO 2004 WHO RCC CLASSIFICATION

The classifications can be different depending on their objective and the different ways of thinking through the time. The mechanical model of disease and the limited therapeutic modalities (practically only surgery) gave for a long time a classification with a few histological subtypes. With the introduction of the new therapies and the study of the familial RCC [11] some molecular pathways are incorporated to the RCC. For all of these considerations emerges the latest WHO's 2004 classification [12] that combines the morphological and genetic characteristics and starts to recognise some variations with evidences of different immunophenotype or molecular changes with clinical implications.

The WHO's 2004 classification (**Table 1**) makes a clear distinction between certain tumour subtypes having better prognosis, and others that do not. The differences regarding prognosis of the most usual forms is statistically significant at the univariate studies [13, 14], but it has no independent statistical significance in some other studies [15]. In spite of this, some cell subtypes do seem to be related to different carcinogenesis [16], and their response to future therapies may be different too [17].

Table 1: WHO HISTOLOGICAL CLASSIFICATION OF RCC

Clear cell renal cell carcinoma
Multilocular clear cell renal cell carcinoma
Papillary renal cell carcinoma
Chromophobe renal cell carcinoma
Carcinoma of the collecting ducts of Bellini
Renal medullary carcinoma
Xp11 translocation carcinomas
Carcinoma associated with neuroblastoma
Mucinous tubular and spindle cell carcinoma
Renal cell carcinoma, unclassified

III. HEREDITARY AND FAMILIAL RCC

Each tumour type presents a special histological spectrum of phenotypes which is accompanied by the expression of a certain spectrum of antigens that can be detected immunohistologically (among others for differential diagnostic purposes).

Nearly each renal cell tumour type occurs in a sporadic or in a hereditary form [18]. A surprising number of hereditary syndromes predisposes to the development of renal cell carcinoma. Within the last years 7 renal cancer syndromes have been characterized. Five of the predisposing genes have meanwhile been identified: VHL, MET, FH, BHD, and HRPT2 (Table 2).

VHL disease is the most frequent familial renal cancer syndrome and is associated with clear cell renal carcinoma and multi-organ neoplasia, escorted by mutations in the VHL gene and loss of the wild-type VHL-allele. The von Hippel-Lindau syndrome is estimated to occur at rates of 1:36.000 to 1:45.500 population. The typical renal manifestation of VHL are kidney cysts and renal clear cell carcinomas. Multiple kidney tumors of other histological types rule out the diagnosis of VHL syndrome. Histological examination of macroscopical inconspicuous renal tissue from VHL-patients may reveal several hundred independent tumors and cysts. The mean age of manifestation is 37 years versus 61 years for sporadic clear cell renal carcinomas, with an onset age of 16 to 67 years. Metastatic RCC is the leading cause of death from VHL. The median life expectancy of VHL-patients was 49 years. In order to detect VHL-associated tumors in time, analysis of germ line mutations of the VHL-gene have been recommended in every patient with retinal or CNS hemangioblastoma, particularly of those in younger age and with multiple lesions. Germ line mutations of the VHL-gene are spread all over the 3 exons. Missense-mutations are most common, but nonsense-mutations microdeletions/insertions, splice mutations and large deletions also occur. The spectrum of clinical manifestations of VHL reflects the type of germ line mutations. Phenotypes are based on the absence (type 1) or presence (type 2) of pheochromocytoma. VHL type

2 is usually associated with missense-mutations and subdivided on the presence (type 2a) or absence (2b) of renal cell carcinoma. In contrast to loss of functions variance in VHL type 1, mutations predisposing to pheochromocytoma (VHL type 1) are mainly of the missense type predicted to give rise to conformationally change of pVHL. In addition, VHL type 2c has been used for patients with only pheochromocytoma; however several years later some of these cases developed other VHL manifestations.

Patients with hereditary papillary renal carcinoma (HPRC) have a germline-activating mutation in the MET-proto-oncogene which can cause renal cancers with papillary type-1 histology. Papillary type-2 renal carcinomas and uterine smooth-muscle tumors are associated with hereditary leiomyomatosis and renal cell cancer syndromes (HLRCC), which is caused by germline loss-of-function mutations in the Fumarate-Hydratase (FH) gene. The hyperparathyroidism-jaw tumor (HPT-JT) syndrome is associated with parathyroid adenomas, fibro-myalgic tumors of the jaw and renal tumors. This syndrome is caused by germline mutations in the HRPT2. The Birt-Hogg-Dubé syndrome (BHD) is associated with an increased risk for renal cancers of various histological types, such as chromophobe RCC and oncocytic hybrid tumors.

With respect to these findings the cytogenetic background of renal carcinogenesis became more important as questions of an adenoma / carcinoma sequence and initiation steps and tumour progression were analyzed. It should be noted that this research is still going on and is completed by new molecular genetic results.

Based on the knowledge of these different cytogenetic pathways there was an intensive research for molecular changes that were associated with these chromosomal aberrations. This finally led to some important tumour suppressor genes like the von Hippel-Lindau gene in clear cell carcinoma etc and oncogenes that are involved in cell cycle regulation and differentiation.

Between 24-45% of VHL patients develop clear cell renal cell carcinoma (ccRCC). Inactivating germline mutations of the VHL gene represents the genetic hallmark of this syndrome and have been demonstrated in almost all VHL patients. Sporadic clear cell RCC (the most frequent subtype of sporadic renal cancer [18]) is characterized by inactivation of the VHL gene by deletion, mutation or promoter hypermethylation in about 70% of the tumors.

The functions of the VHL protein (pVHL) have been extensively studied in the last 15 years. The VHL protein (pVHL) is implicated in cell-cycle control and gene regulation, and requires transcription-dependent nuclear-cytoplasmic trafficking for its

Table 2: Hereditary renal cell tumours

syndrome	chr.	gene	protein	tumour type	extrarenal manifestations	
					Dermis	Other organs
von Hippel-Lindau	3p25	<i>VHL</i>	pVHL	multiple, bilateral clearcell RCC, renal cysts	-	hemangioblastoma of retina / CNS; pheochromocytoma; pancreatic/renal cysts; neuroendocrine tumours; epididymal / parametrial cysts; tumours of the inner ear
hereditary papillary RCC	7p31	<i>MET</i>	HGF-R	multiple, bilateral papillary RCC (type 1)	-	-
HLRC	1q42	<i>FH</i>	FH	papillary RCC (non type 1)	leiomyoma	uterine leiomyoma / leiomyosarcoma
familial papillary thyroid carcinoma	1q21	?	?	papillary RCC, oncocytomas	-	papillary thyroid carcinoma
hyperparathyroidism – jaw tumour (HP-JT)	1q25	<i>HRPT2</i>		epithelial-stromal mixed tumours, papillary RCC	-	tumours of the parathyroid; fibro-osseous jaw tumours
Birt-Hogg-Dubé	17p11	<i>BHD</i>	Folliculin	multiple chromophobe RCC, oncocytic adenoma, papillary RCC	Facial fibrofolliculoma	pulmonary cysts; spontaneous pneumothorax
tuberous sclerosis	9q34 16p13	<i>TSC 1</i> <i>TSC 2</i>	Hamartin Tuberlin	multiple, bilateral angiomyolipomas, lymphangiomyomatosis; rare clear cell RCC	angiomyofibroma; peau chagrin; subungual fibroma	cardiac rhabdomyoma; adenomatous small intestine polyps; pulmonary / renal cysts; cortical tuber; subependymal giant cell astrocytomas
constitutional translocation chr. 3	3p13-14	?	?	multiple, bilateral clear cell RCC	-	-

function. There are two biologically active VHL protein isoforms: pVHL[30] and pVHL[19]. The distribution of VHL protein isoforms varies in the nuclear and cytoplasmic compartments of renal tumors and alteration of subcellular pVHL trafficking is of potential relevance for the biological behaviour of clear-cell RCC [19, 20].

The pVHL functions as a recognition subunit in a E3 ubiquitin protein ligase complex, targeting the hypoxia-inducible transcription factor a (HIF- α) for ubiquitin mediated degradation in the presence of

oxygen [21]. Under normoxic conditions, hypoxia-inducible factor-1 (HIF-1) is hydroxylated (-OH) on two conserved proline residues by a family of prolyl hydroxylases at its oxygen-dependent degradation domain. This hydroxylation provides a substrate-recognition site for the von Hippel-Lindau (VHL) E3 ubiquitin ligase complex which contains elongins C and B, cullin-2 (CUL2) and RBX1. Polyubiquitylation of HIF-1 by the VHL complex leads to its proteasomal degradation by the 26S proteasome. Hypoxic conditions block hydroxylation, allowing HIF-1

subunits to accumulate and activate transcription of hypoxia-responsive genes. VHL inactivation — as occurs in renal cells from patients with a germline VHL mutation and loss of the wild-type allele — mimics the hypoxic response by preventing degradation of HIF-1 subunits. Loss of VHL function causes accumulation of HIF-1 subunits in the cytoplasm and their translocation to the nucleus. HIF-1 dimerizes with HIF-1 and is coactivated by CBP/p300. HIF binds to hypoxia response elements (HRE) in gene promoters, thereby activating transcription of genes upregulated in clear-cell renal tumours, including a vascular endothelial growth factor (VEGF), erythropoietin and platelet-derived growth factor. Clear cell RCC is characterized by rich neo-vascularization and an often prominent vascular network around tumor cells, suggesting the elaboration of tumor angiogenesis factors by neoplastic cells. It has been demonstrated that strong vascularization in ccRCC is correlated with VEGF expression, suggesting that this growth factor plays a role in the vascular biology of ccRCC tumors as a consequence of VHL inactivation [22]. VEGF stimulates endothelial cell proliferation *in vitro* and has also an angiogenic activity *in vivo*.

Recently, it was shown that loss of VHL function results in strongly enhanced transcription of HIF- α inducible genes, especially in up-regulation of CXCR4 [23]. Therefore, the von Hippel-Lindau (VHL) tumor suppressor gene product is one of the major regulators of CXCR4 expression and increased CXCR4 expression levels are most likely a consequence of impaired VHL function in ccRCC. Strong CXCR4 expression is associated with poor prognosis of RCC. Thus, by expressing CXCR4, tumors obviously acquire properties, which enable them to invade tissue barriers, migrate to secondary organs, and form metastases. Although CXCR4/CXCL12 expression patterns may explain selection of specific organs for the formation of metastasis, the exact molecular mechanisms by which the CXCR4/CXCL12 axis promotes tumor invasion are still unclear.

Other pVHL functions include fibronectin matrix assembly, p53 stabilization and transactivation [24, 25]. In addition, pVHL has the ability to bind and stabilize microtubules by protecting them from depolymerization, which is a prerequisite for cilium formation [26]. In fact, two previous *in vitro* studies showed that by re-expressing pVHL in VHL null ccRCC cell lines pVHL regulates the formation of primary cilia [27, 28]. These observations strongly suggest that loss of VHL function in renal epithelial cells leads to degeneration of primary cilia, which represents a critical step towards cyst formation and ccRCC development in VHL patients. Interestingly, renal cysts are also present in about 60% of individuals suffering from the von Hippel-Lindau (VHL) disease. One might hypothesize that cyst

formation is one of the first visible renal alterations in VHL-caused tumor formation.

The elucidation of the different pVHL functions is the basis for understanding the novel therapeutic strategies for RCC patients [29]. Targeting the VHL pathway for therapeutic intervention can theoretically occur at many sites. VHL protein function could be replaced, restoring binding to hypoxia-inducible factor-1 (HIF-1) and allowing its proteasomal degradation. Further, the activity of HIF-1 could be a target for inhibition. Finally, molecules upregulated by HIF-1 (e.g. CXCR4) also provide specific targets for potential downstream inhibition of the VHL pathway.

IV. CLEAR CELL RENAL CELL CARCINOMA

Tumours are usually single in the sporadic cases, with 4% multiplicity and 3% bilaterality. The tumour is well delimited by pseudocapsule of fibrous tissue that is the consequence of compression of the surrounding tissues. Due to cytoplasm lipids accumulation the section surface is yellow. Haemorrhagic areas are frequent for the large vascular stroma. Occasionally there are scar areas and some of them even include calcification. Necrosis is associated with more aggressive neoplasias.

The cystic appearance it sometimes adopts may be due to necrosis and liquefaction (pseudo-cysts) or because it is formed by genuine neoplastic cysts.

Among the cystic renal cell carcinomas there are cases of clear cell renal cell carcinomas with a wide cystic transformation, as well as cases with complete cystic appearance that lack a solid tumoral component.

The latter subtype has been called **multilocular cystic renal cell carcinoma** [30]. The cysts' wall exhibit isolated malignant cells (**Fig. 1**). Macroscopically their appearance may be similar to that of a multilocular cyst (cystic nephroma). The excellent prognosis in a recent multi-institutional study suggests the possibility of considering it a low-malignant-potential carcinoma [31].

1. MICROSCOPY

As suggested by its name, this neoplasia consists of clear cytoplasm cells; they are clear due to their high content of glycogen and lipids that dissolve in the course of the histologic processing. Cells with a higher mitochondrial content may be seen to acquire an eosinophilic or granular appearance (**Fig. 2**). The predominance of this cell type is exceptional. Rounded or irregular eosinophilic cytoplasm inclusions are rarely found. The nuclei are rounded and their characteristics depend upon their degree of differentiation. The most frequent arrangement forms

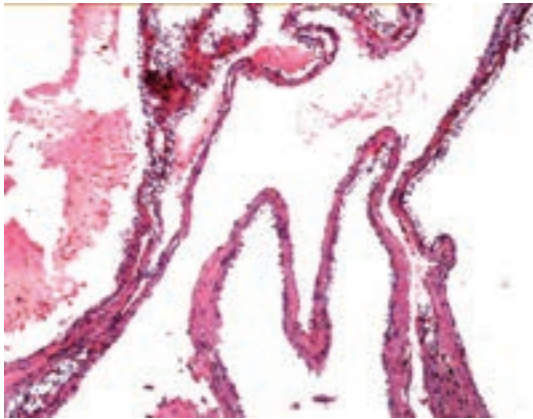


Fig. 1A .- Cystic neoplasms with clear cell in the wall



Fig. 1B.- Fibrous wall with clear cells.

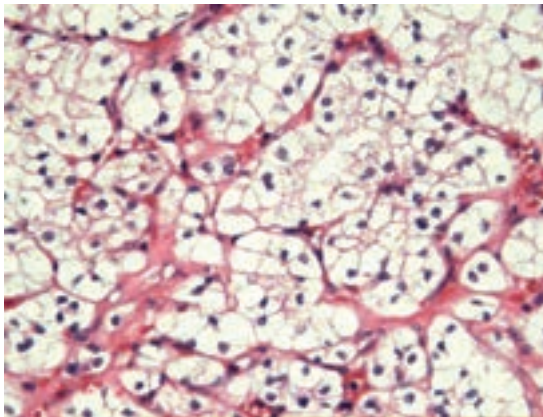


Fig. 2A.- Clear cell renal cell carcinoma

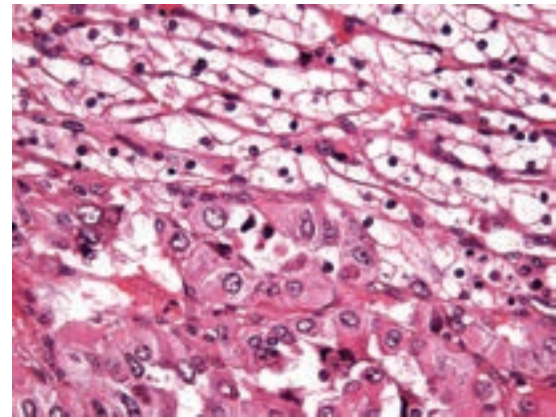


Fig. 2B.- Eosinophilic cells (high grade) in clear cell renal cell carcinoma

a solid pattern. Tubular and occasionally microcystic patterns can also be present. Papillary areas are very rarely observed [32]. Five percent of cases are of the spindle cell (sarcomatoid) type [33].

2. IMMUNOPHENOTYPE

The cells express more frequently low molecular weight cytokeratins (CAM 5.2 around 60%) than high molecular weight cytokeratins (CK14 in 3.7%) [34]. Vimentin is expressed in 82.6% [35], CD10 in 94% (**Fig. 4**) and RCC antibody in 85% [36]. Epithelial membrane antigen (EMA) (MUC-1) in 85% [37]. Glutathione S-transferase α (GST- α) in 82% [38]. From adhesion molecules there is only 5% of E-cadherin [37] and Kidney-specific cadherin (Ksp-cadherin) is negative [39]. Paraalbumin is expressed in 26% and β -Defensin-1 in 13% [35]. Other markers such as c-kit, RON proto-oncogene and p504S – alpha-methylacyl-CoA racemase (AMACR) are virtually negative [40, 41, 42].

3. GENETIC CHANGES

3p deletion (LOH 3p) is the most typical genetic

abnormality of this carcinoma, present in 75.8% of cases [43], but not exclusive to it [44]. Three genes have been located on the short arm of chromosome 3 that are probably involved in renal carcinoma. The suppressor gene in 3p25-26 (VHL) which coincides with von Hippel-Lindau disease but is expressed in 34-56% of sporadic carcinomas [45], and those located on 3p14.2 (potential gene FHIT) and on 3p.12, whose deletion is more frequent than of the former. Other putative tumour suppressor genes at 3p as RASSF1A and NRC-1 at 3p12 are reported [46, 47].

LOH 3p interferes with the hypoxia-inducible pathway that activates VEGF and PDGF, both of which play an essential role in angiogenesis, glucose transport, glycolysis, pH control, epithelial proliferation, cell migration and apoptosis, and can help the hypoxic adaptation of the clear cell carcinoma [48]. Therefore, a therapeutic multi-targeted approach that selectively and simultaneously blocks these growth factors represents an attractive way of treatment [49, 50].

V. PAPILLARY RENAL CELL CARCINOMA MORPHOLOGY CRITERIA FOR PATHOLOGICAL DIAGNOSIS.

Tumors with a diameter up to 5 millimeters are considered adenomas [12]. They are often incidental findings and occur in up to 23% of autopsy patients. The larger tumors are viewed as carcinomas, comprises the 15% of all of surgically removed renal cell neoplasms and its male to female ratio is 2:1[12].

Papillary renal cell neoplasms are grossly characterized by a spherical boundary and a beige to white colour. They can exhibit central necrosis resulting from a poor vascular supply and frequent hemorrhages. In some cases this feature can be so extensive to mimic a cyst both radiologically and grossly [51].

Papillary renal cell neoplasms are characterized by papillary or tubulo-papillary architecture. The epithelial neoplastic cells line a delicate fibrovascular core in which aggregates of foamy macrophages can be found. The core can be expanded by edema. In carcinomas cholesterol crystals, necrosis and haemorrhage are frequently seen and haemosiderin granules may be present in macrophages, stroma and tumour cell cytoplasm. Sarcomatoid dedifferentiation is seen in approximately 5% of papillary renal cell carcinomas [51]

1. PATHOLOGICAL SUBTYPES

Two well recognized morphological types of papillary renal cell carcinomas have been described [52]: Type 1 tumours have papillae covered by small cells with scanty cytoplasm, arranged in a single layer on the papillary basement membrane with low nuclear grade (Fig. 3); Type 2 tumours are composed by cells with higher nuclear grade, eosinophilic cytoplasm and pseudostratified nuclei on papillary cores (Fig. 4). Type 1 tumours are more frequently multifocal. Psammoma bodies are common. Longer survival has been described for type 1 papillary renal cell carcinoma when compared with type 2 [54]. Papillary renal cell carcinomas entirely composed by oncocytes has been described [54, 55, 56, 57, 58]. This subset of papillary tumors shows clinico-pathologic features different from type 1 and type 2 papillary renal cell carcinomas and has been proposed to be referred as a third group, being the outcome intermediate between type 1 and type 2 [54, 55, 56, 57, 58].

There are emerging groups of papillary renal carcinoma showing at a cytologic level a wider spectrum than that already recognized. Oncocytic papillary renal cell carcinoma are composed of

papillary structures with delicate fibrovascular stalks containing, occasionally, crowded lipid-laden foamy macrophages. The papillae are lined by single or, more rarely, pseudostratified layers of cells with granular, deeply eosinophilic cytoplasm with distinct cell border. The nuclei were round with frequently prominent nucleoli conforming to a nuclear grade 3. Solid areas with morphological features overlapping typical renal oncocytoma are often observed [54, 55, 56, 57, 58].

Papillary renal cell carcinoma with clear cell changes is a neoplasm composed of papillary structures covered by medium-sized cells with clear cytoplasm made up 20% to 90% of the total neoplastic area. The tumor cells show variable degrees of cytoplasmic clarity; often, the cytoplasm has a microcicular or finely granular appearance similar to the cytoplasm of foamy macrophages that were frequently present within papillary cores and in spaces between the papillae. Usually, the nuclei are positioned centrally or basally, and nuclear grade is quite homogeneous throughout the neoplasms [32, 59, 60].

Spindle cell areas in papillary renal cell carcinoma generally signify sarcomatoid change and are high grade. It has been reported that low-grade spindle cell foci, closely mimicking mucinous tubular spindle cell carcinoma can occur. These tumors are predominantly solid, featuring compact areas of low-grade spindle cells lining thin, angulated tubules. Mucinous stroma was not appreciated in any case [61].

2. IMMUNOHISTOCHEMICAL FEATURES

Reaction for cytokeratin 7 was strong or moderate in 48 of 61 Type 1 tumors, and reaction was null in 24 of 30 Type 2 originally described tumors [52].

The neoplastic oncocytic cells of oncocytic papillary renal cell carcinoma in all cases described, exhibited strong, diffuse, and granular positivity for antimitochondrial antigen reaction and for AMACR (Fig. 5). Tumoral cells demonstrated variable positivity for cytokeratins, AE1/AE3, CK8-18, CK7, CK19, EMA and CD10 was positive in 10 cases. There was diffuse positivity for vimentin and some cases were positive for paraalbumin [54].

Papillary renal cell carcinoma with clear cell changes showed strong immunoreactivity for AMACR, of which a subset also expressed cytokeratin 7 such as all cases of spindle cell papillary renal cell carcinomas reported [59].

3. MOLECULAR/GENETIC FEATURES

Papillary renal cell carcinoma is characterized by trisomy of chromosomes 3q, 7, 8, 12, 16, 17 and 20 and loss of the Y chromosome [62]; these most consistent genetic abnormalities are present in both solitary and multifocal papillary renal cell

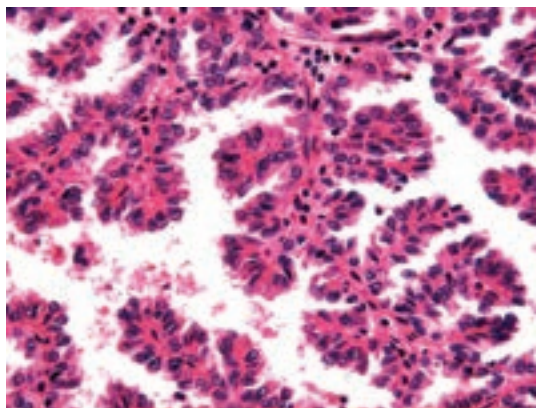


Fig. 3.- Papillary renal cell carcinoma type I, basophilic cells

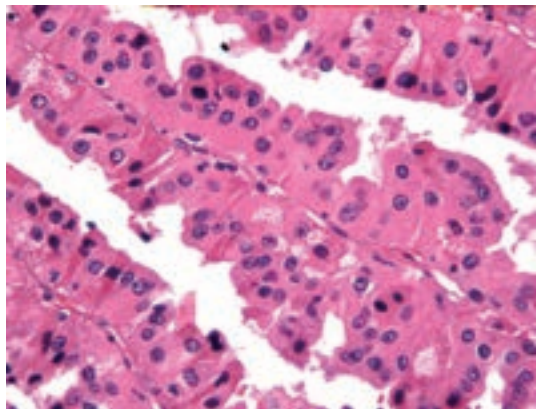


Fig. 4.- Papillary renal cell carcinoma type II, eosinophilic cells with high grade

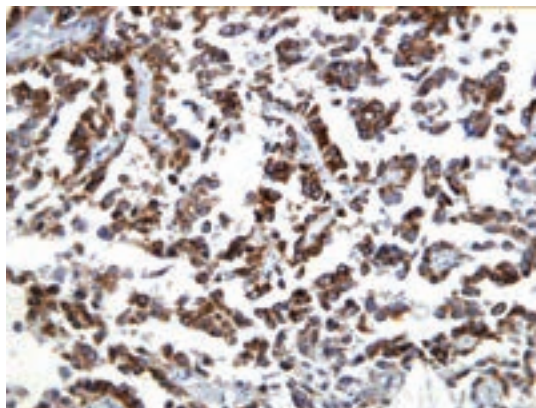


Fig. 5.- AMACR expression in papillary renal cell carcinoma.

carcinomas and they occur early in the evolution of this neoplasm[62]. Some authors have suggested genetic differences between type 1 and type 2; type 1 papillary renal cell carcinoma cases seem to have a significantly higher frequency of allelic imbalance on 17q than type 2 cases and type 2 cases an higher

frequency of allelic imbalance on 9p than type 1 cases [63, 64]. The c-Met proto-oncogene mutation on chromosome 7 characterizes hereditary and a subset of sporadic papillary renal cell carcinomas [65]. Patients with the hereditary leiomyomatosis and renal-cell cancer syndrome are at risk for cutaneous and uterine leiomyomas and solitary papillary renal-cell carcinoma with type 2 histologic features [66]. Fumarate hydratase gene, the gene that causes this autosomal dominant syndrome, encodes fumarate hydratase, a Krebs-cycle enzyme [67].

Among oncocytic papillary RCCs, three or more signals were frequently observed in the tumor cells: chromosomes 7 (range, 3%-74%; 30% in 7 of 12) and 17 (range, 6%-69%; 80% in 7 of 12). In 5 cases, three or more signals for both chromosomes were found. No signal for Y was observed in 80% to 90% of nuclei in 3 tumors of the 10 males [54].

Among 14 papillary renal cell carcinoma with clear cell changes, most neoplasms exhibited gains of chromosome 7; nine showed gains of chromosome 17 and 4 neoplasms from 6 male patients showed loss of chromosome Y.¹⁰ Chromosome 3p deletion was detected in 4 cases. FISH analysis from areas of papillary renal cell carcinoma and from areas with clear cell morphology in the same tumor showed similar results [59].

All spindle cell papillary renal carcinomas reported showed trisomy of chromosome 7, and 3 of 5 showed trisomy of chromosome 17 [61].

4. DIFFERENTIAL DIAGNOSIS

Papillary renal cell carcinoma is the tumour that most frequently may exhibit overlapping characters with other subtypes of renal cell carcinoma. Clear cell renal carcinoma, which is the most frequent renal cell neoplasms, may show pseudo-papillary structures; in this context the immunoprofiling characterized by the immunoreactivities for AMACR and cytokeratin 7 and the gains of chromosomes 7 and 17 are usually mandatory to classify the neoplasms as to be papillary subtype. The solid variant of papillary renal cell carcinoma may show overlapping features with serous renal neoplasms in particular with the metanephric adenoma whereas the oncocytic variant encounters in the differential diagnosis the renal oncocytoma; again the gains of both chromosomes 7 and 17 are present in this papillary subtype.

The group of papillary renal cell carcinoma is extremely heterogeneous in particular in the subset of neoplasms classifiable as type 2 probably including cases of clear cell renal cell carcinoma with pseudopapillary tubulo-glandular architecture and high nuclear grade, cases of translocation carcinoma and Bellini duct carcinoma.

VI. CHROMOPHOBE RENAL CELL CARCINOMA

Chromophobe renal cell carcinoma (CRCC), a renal cell carcinoma of low malignant potential characterized by huge pale cells with prominent cell membranes, was initially described in nitrosamine-induced renal tumours in rats. The first cases of CRCC in humans were reported in 1985. CRCC accounts for approximately 5 per cent of surgically removed renal epithelial tumors [71]. The median/mean age of incidence is in the sixth decade, with a range in age of 27 to 86 years, and the number of men and women is roughly equal. Mortality is less than 10 %. Sporadic and hereditary forms do exist.

1. MACROSCOPIC APPEARANCE

Depending on size, chromophobe renal cell tumors consist of one or more solid tumor nodules with a slightly lobulated surface. In unfixed conditions the cut surface appears homogeneously orange turning beige or sandy after formalin fixation. The uniform pale cut surface interspersed with a few hemorrhages is a very characteristic gross feature, while a slight brown colored cut surface is usually seldom.

2. HISTOPATHOLOGY

The basic chromophobe cell type is characterized by large polygonal cells with a transparent slightly reticulated cytoplasm for numerous sometimes innervated vesicles, 150-300 nm in diameter resembling those of the intercalated cells type b of the cortical collecting duct, with prominent cell membrane leading to a plant cell like appearance (Fig. 6). The perivascular cells are often enlarged. An eosinophilic variant does exist (Fig. 7), it is purely composed of intensely granular large and small cells with prominent cell membranes [70]. Sarcomatoid/spindle cell transformation does occur (Fig. 8) [72]. Another diagnostic hallmark is the lack of cytoplasmic coloring with routine dyes but a diffuse cytoplasmic staining reaction with Hale's iron colloid stain (Fig. 9). Chromophobe cells usually show condensed and hyperchromatic sometimes binucleated nuclei. In general, the growth pattern is solid/compact, sometimes cribriform associated with focal calcifications and broad fibrotic septae. The so called hybrid tumors share histopathological characteristics of chromophobe carcinoma and oncocytic adenoma as both cell types are intermingled. Fuhrman grading seems not to be appropriated to grade chromophobe RCC.

3. IMMUNOPROFILE

Immunohistochemistry presents the following antigen profile: Pan-Cytokeratin +, Vimentin -, EMA + (diffuse), lectins +, Parvalbumin +, RCC-antigen -/+, CD 10 -. CRCC presents significant hypodiploid cell clones with flow cytometry and quantitative image analysis of DNA ploidy.

4. CYTOGENETICS AND MOLECULAR ALTERATIONS

Renal cell carcinomas of the chromophobe type are cytogenetically characterized by a massive loss of chromosomes, i.e. -1,-Y,-2,-10,-6,-21,-13, and -17. These data are confirmed by FISH- and CGH analyses [68, 69].

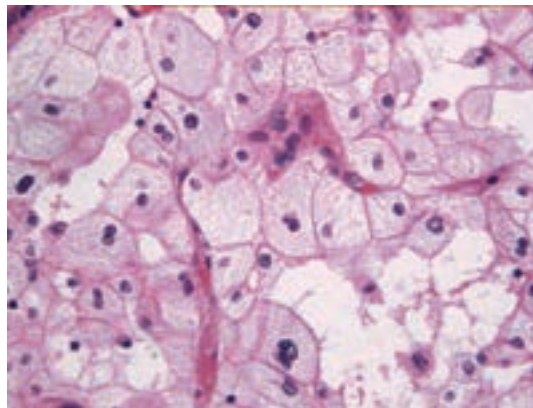


Fig. 6.- Chromophobe renal cell carcinoma, clear cell type

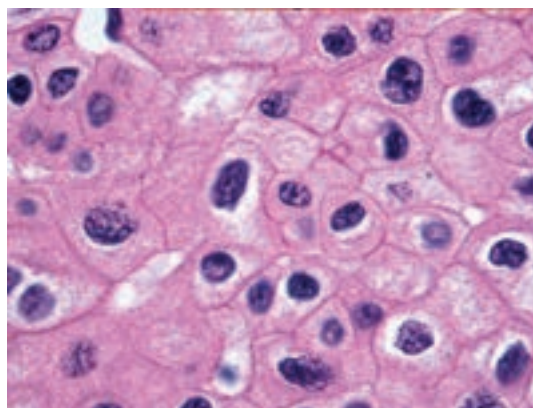


Fig. 7.- Chromophobe renal cell carcinoma, eosinophilic type.

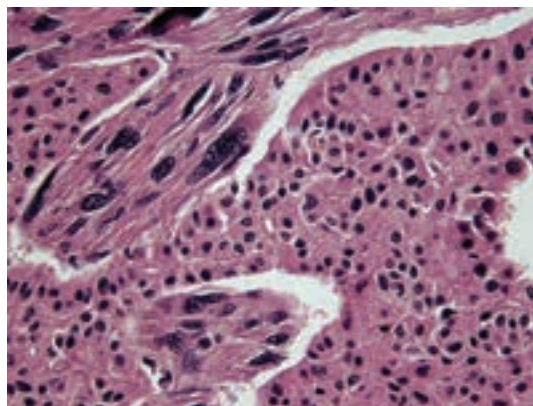


Fig. 8.- Chromophobe renal cell carcinoma of high grade with sarcomatoid component.

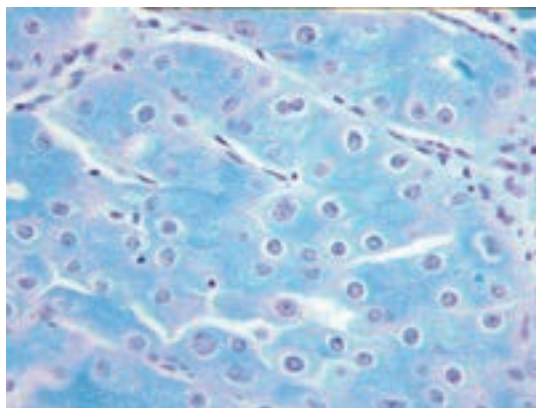


Fig. 9.- Hale's iron staining in chromophobe renal cell carcinoma.

Cytogenetic and molecular genetic data on chromophobe renal cell carcinoma (RCC) is limited, possibly due to their general tendency to grow very slowly in vitro compared to all other type of renal tumors. Karyotyping, fluorescence in situ hybridization, comparative genomic hybridization, and microsatellite analyses have revealed that multiple and nonrandom chromosomal losses, i.e. monosomies of chromosomes 1, 2, 6, 10, 13, 17, 21, and the Y or X chromosome are pathognomonic for chromophobe RCC. Additional structural chromosomal aberrations have been described, but no (partial) loss of the short arm of chromosome 3. The massive chromosomal losses lead to a hypodiploid DNA index (low modal number of chromosomes). Endoreduplication/polyploidization of the hypodiploid cells has been observed. Telomeric associations and telomere shortening have also been observed. Furthermore, molecular analysis of this subtype has revealed gross alterations of the mitochondrial DNA. Nagy et al. found somatic mitochondrial DNA mutations, although their exact role remains to be elucidated.

At the molecular level, Contractor et al. showed an association between loss of chromosome 17 and mutation of *TP53* tumor suppressor gene in 27% of the chromophobe RCCs. Süß et al. demonstrated loss of heterozygosity (LOH) around the *PTEN* gene at the 10q23.3 chromosomal region. However, deletional or mutational inactivation of the *PTEN/MMAC1* gene could be excluded.

The finding of mitochondrial DNA changes and the loss of Y/X and chromosome 1 in both renal oncocytoma and chromophobe carcinoma might indicate progression from renal oncocytoma to chromophobe renal cell carcinomas the malignant counterpart of renal oncocytoma through additional chromosome losses, also explaining the occasionally malignant behavior of renal oncocytomas. With respect to hereditary RCC, no families have been reported with members affected with chromophobe renal carcinomas.

Familial clustering is unknown. There is an inherited cancer syndrome called Bird-Hogg-Dube-Syndrom (BHD), which is an autosomal dominant disease characterized by trichofolliculomas, trichodisomas and lung cysts. The BHD-gene is localized on the short arm of chromosome 17.

Brunelli et al. studied a large number of classic and eosinophilic chromophobe RCCs and showed that the eosinophilic variant of chromophobe renal cell carcinoma and classic chromophobe renal cell carcinoma have similar frequency of losses of chromosomes 1, 2, 6, 10, and 17, consistent with the notion that these tumors are simply morphologic variants of the same neoplasm.

The mechanisms of the histopathologic changes during the development of chromophobe RCC is unknown, but the characteristic chromosomal losses are helpful in establishing an accurate diagnosis.

5. MAJOR DIFFERENTIAL DIAGNOSIS

- **Renal oncocytoma.** Chromophobe renal cell carcinomas, especially the eosinophilic variant, are frequently difficult to distinguish from renal oncocytomas on hematoxylin and eosin stained histologic sections. The distinction is important, as chromophobe renal cell carcinoma is a malignant tumor while oncocytoma is considered to be a benign lesion. Reports of "malignant" or "metastatic" oncocytomas are postulated to actually represent misdiagnosed chromophobe renal cell carcinomas. The Hale's colloidal iron stain shows a diffuse and strong reticular pattern in almost 100% of chromophobe RCC. Chromophobe renal cell carcinomas frequently show loss of chromosomes 1 (70% of classic, 67% of eosinophilic), 2 (90% classic, 56% eosinophilic), 6 (80% classic, 56% eosinophilic), 10 (60% classic, 44% eosinophilic), and 17 (90% classic, 78% eosinophilic). 44% of eosinophilic chromophobe renal cell carcinomas exhibit loss of all five of these chromosomes. Genetic alterations of oncocytoma have not yet been well characterized. However, renal oncocytomas have been reported to bear either rearrangements or translocations involving chromosome 11q13[86] or partial or complete losses of chromosomes 1, 14, and/or a sex chromosome (Y or X). Several groups of investigators have reported that chromosome 3p loss is not detectable in oncocytoma. Because of the frequent association between oncocytomas and chromosome 1p alterations, the loss of a tumor suppressor gene residing on chromosome 1p has been proposed as the earliest genetic event associated with the development of renal oncocytoma. Oncocytomas have also been shown to exhibit microsatellite instabilities. Alterations in mitochondrial DNA have also been implicated in the development of oncocytomas. It is noteworthy that there are no apparent overlapping genetic alterations shared by eosinophilic chromophobe

renal cell carcinoma and oncocytoma, despite their morphological similarities. It has been postulated that eosinophilic chromophobe RCC originates from renal oncocytoma, and represents the malignant form of this tumor.

- **Renal oncocytosis** Renal oncocytosis is characterized by the presence of multiple tumors with oncocytic features, often associated with small clusters of tubule-like structures with oncocytic change. Cossu-Rocca et al studied 11 tumors from the kidney of one such patient. Fluorescence in situ hybridization was performed with centromeric probes for chromosomes 1, 2, 6, 10, and 17 in each of the 11 tumors. All 11 tumors from this patient with renal oncocytosis showed no loss of any of the chromosomes 1, 2, 6, 10, or 17, a pattern identical to that found in normal control tissues. Therefore the chromosomal profile may be the diagnostic procedure of choice for distinguishing between chromophobe RCC and renal oncocytosis.

6. PROGNOSIS

The large majority of CCRCs are stage T1 and T2 (86%) whereas only 10% show extension through the renal capsule into surrounding adipose tissue, only 4% show involvement of the renal vein (T3b). A few cases of well-documented distant metastasis (lung, liver and pancreas) have been described. No lymph node metastases have been reported yet. Spindle cell phenotype is associated with aggressive tumour growth/metastasis. Genetic predictive factors are not known.

VII. COLLECTING DUCT CARCINOMA, RENAL MEDULLARY CARCINOMA

Renal collecting duct, or Bellini's duct, carcinoma (CDC) is a relatively rare subtype of renal cell carcinoma (RCC), accounting for 0.4% to 1.8% [73, 74] of all RCCs in Western countries. In Japan, the Japanese Society of Renal Cancer reported that a Nationwide survey of CDC from 2001 to 2003 [75]. In this survey that was the largest case series to consider outcome to date, 81 cases were counted from 281 institutions throughout Japan. The incidence of CDC in Japan was considered as less than 1.5%, because each institution experienced more than 10 patients with RCC per year. Several studies have shown a male predominance and a tendency for this disease to occur more frequently in relatively younger adults. Japanese survey showed that the median age was 58.2 years and males comprised 71.6% of the patient population. According to Japanese survey, regional lymph node metastases were present in 44% of the patients at diagnosis, whereas distant metastases were seen in 32%. The 1-, 3-, and 10-year disease-specific

survivals were 69%, 45%, and 14%, respectively.

Renal medullary carcinoma (RMC) is a relatively new subtype of RCC that is thought to arise from the calyceal epithelium. It has been first seen and is still detected almost exclusively in individuals with sickle cell trait or anemia. This tumor shares many histologic features with CDC, and some consider it a subtype of CDC or at least a closely related tumor. Although relationship between these two entities still remains controversial, most recently RMC is considered to differentiate from CDC [74, 76].

1. MORPHOLOGICAL CRITERIA FOR PATHOLOGICAL DIAGNOSIS

CDCs are derived from the medulla, but many are infiltrative and extension into the cortex is common. Typically CDCs are white to gray and have a firm consistency on sectioning. Histologically, CDC is characterized by a tubulopapillary architecture, which consists of an admixture of dilated tubules and papillary structures typically lined by a single layer of cuboidal cells, often creating a cobblestone appearance and associating with desmoplastic stromal reaction (Fig. 10). On the other hand, it has been reported that most common histologic appearance of RMC is cribriforming glands surrounding by a desmoplastic reaction. Both CDC and RMC are considered to be somewhat similar to poorly differentiated urothelial carcinoma.

2. MOLECULAR/GENETIC FEATURES

In CDCs, trisomy for chromosomes 4, 7, 8, 17 and 20 and loss of chromosomes 14, 18 and 22 were reported [77]. Another analysis showed monosomy of chromosomes 1, 6, 14, 15 and 22 [78]. Loss of heterozygosity of 8p and 13q has been reported in further studies [79]. The most constant change would be 1q32 deletion (80, 81). The molecular pathogenesis of CDC is not known. Although loss of chromosome 3p, including VHL gene was not common in CDC [79], some literatures have described that activation of VEGF signaling, which

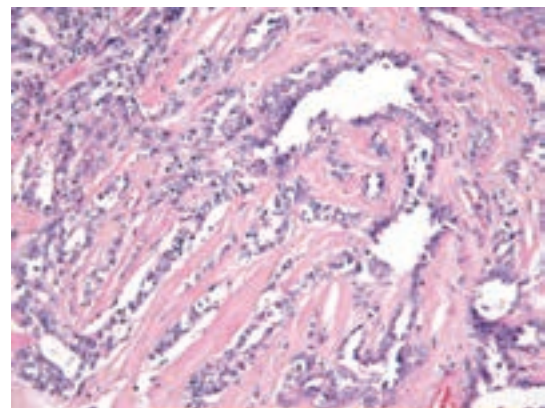


Fig. 10.- Collecting duct carcinoma with desmoplastic reaction

is analogous to the clear cell RCC hypothesis a pathway may be related to RMC carcinogenesis [76, 82].

3. IMMUNOHISTOCHEMICAL FEATURES

On immunohistochemistry, the characteristic feature is co-expression of low- and high-molecular weight cytokeratins (cytokeratin 34bE12) and positive reaction to lectins such as *Ulex europaeus* agglutinin-1 (UEA-1) [73, 77, 83]. Kobayashi N, et al. [84] have described that CDC expresses E-cadherin, c-KIT in addition to UEA-1 and cytokeratins. There is a variable expression of Leu M1 and EMA, whereas markers of proximal renal tubules are almost always negative. Some studies reported that RMC strongly expresses cytokeratin 19 and Topo II alpha [85].

4. DIFFERENTIAL DIAGNOSIS

CDC is frequently difficult to distinguish from RMC, pelvic urothelial carcinoma (UC) with marked renal parenchymal invasion and high-grade papillary RCC. To differentiate CDC from RMC, immunohistochemical and molecular approaches may be useful. The difference between CDC and RMA was found in expression pattern of UEA-1, high-molecular weight cytokeratin, c-KIT, E-cadherin, VEGF, EMA, Her-2neu, and karyotype of chromosomes [74]. Immunohistochemical approach is useful for the differential diagnosis of these renal tumors. Swartz et al. [76] have reported about differential diagnosis between CDC and RMC that characteristic immunohistochemical profile for CDC is positivity for cytokeratin 34bE12 and UEA-1. The cytokeratin 34bE12 marker was negative in RMCs and UEA-1 was present only a minority of RMCs in a focal, patchy distribution. It has been also reported that UEA-1, E-cadherin, and c-KIT are frequently positive in CDC in comparison with papillary RCC, which usually expresses markers for proximal renal tubules, such as CD10, RCC antigen and AMACR [74, 84]. Although invasive UC has similar immunohistochemical features with CDC, it has been also shown that high- and low-molecular-weight cytokeratin are positive at a low frequency compared with invasive UC [84].

VIII. MUCINOUS TUBULAR AND SPINDLE CELL CARCINOMA

1. MORPHOLOGICAL CRITERIA FOR PATHOLOGICAL DIAGNOSIS

This entity, included by the first time in the current WHO classification, [12] is a low-grade carcinoma composed of tightly packed tubules separated by pale mucinous stroma and a spindle cell component (**Fig. 11 and 12**) [12, 61- 98]. It seems to derive from the distal nephron but some authors believe it could be a variant of papillary RCC with proximal tubule

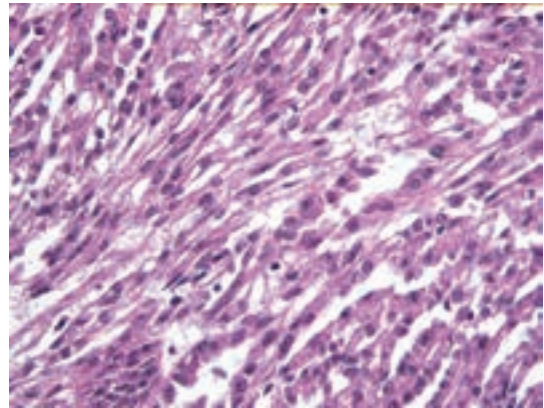


Fig. 11.- Mucinous tubular and spindle cell carcinoma. Tubular and spindle components.

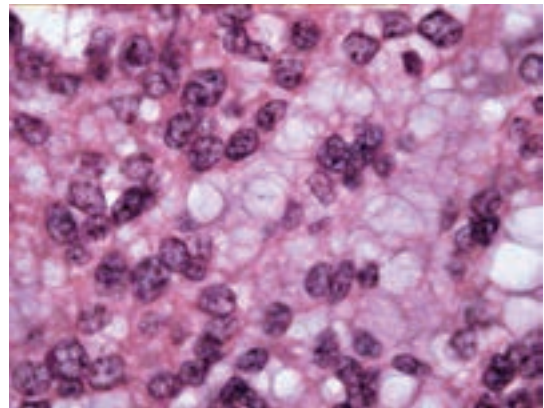


Fig. 12.- Mucinous tubular and spindle cell carcinoma. Mucinous component.

origin[61, 86, 87] There is a female predominance and the mean age is 53 years at diagnosis.[12, 61- 98]. It presents as circumscribed asymptomatic mass on ultrasound examination.[1] Some patients may develop metastases on follow-up. Rare cases showing true, well documented, sarcomatoid change have been recently reported. [88]. Two of these cases occurred in a 71-year-old woman and an 80-year-old man who both underwent a radical nephrectomy procedure. [88]. In addition to the classic mucinous tubular and spindle cell carcinoma (MTSRCC) morphology, both cases had a sarcomatoid component characterized by predominantly high-grade spindle cells, solid pleomorphic epithelioid cells, and malignant fibrous histiocytoma-like storiform patterns [88]. Sarcomatoid change comprised 60% and 20% of the tumors, respectively. One patient died with widespread metastasis.⁵ It is currently considered a poorly defined entity.

2. MOLECULAR/GENETIC FEATURES

This tumor has a variable genetic features and shows a combination of losses involving chromosomes 1, 4, 6, 8, 13, 14 and 15 and gains of chromosomes

2, 5, 7, 9, 10, 11, 12, 16, 17, 19, 20, 22, and X [61, 86-98] Cossu-Rocca et al [89] studied 10 mucinous tubular and spindle cell carcinoma with FISH for chromosomes 7, 17 and Y. They found that renal MTSRCC lacks the gains of chromosomes 7 and 17 and losses of chromosome Y that are typically found in papillary renal cell carcinoma. Rabl et al [90] studied 6 tumors from five patients with CGH and found multiple genetic abnormalities included consistent losses of chromosomes 1, 4, 6, 8, 9, 13, 14, 15 and 22 in all cases. CGH study by Ferlicot et al [91] identified the loss of chromosomes 1, 4, 6, 8, 13, 14, 15 and 18 in a group of MTSRCC.

3. IMMUNOHISTOCHEMICAL FEATURES

A recent immunohistochemical analysis found a significant immunophenotypic overlap with papillary RCC, and some authors believe this is a variant of papillary RCC with spindle cell differentiation [86, 92]. Expression of alpha-methylacyl-CoA racemase (89%), cytokeratin 7 (82%), Vimentin (80%), EMA (78%), 34βE12 (45%) and E-Cadherin (28%), and negativity for CK 14, CD 10, Villin, RCC antigen, c-Kit and Ulex *Europaeus* agglutinin are characteristic of MTSRCC [12, 61- 98]. The proliferative rate in MTSRCC is low (<1%). Some cases of MTSRCC may express neuroendocrine markers, such as NSE and CD57 [93].

4. DIFFERENTIAL DIAGNOSIS

Major histologic differential diagnosis is type I papillary RCC and papillary RCC with solid growth. [12, 61- 98]. A problem further compounded with the description of papillary RCC with low-grade spindle cell foci as a mimic of mucinous tubular and spindle cell carcinoma [61]. All cases in this category were diffusely immunoreactive for cytokeratin 7, and focally CD10 positive. [61]. Also, all 5 cases showed trisomy of chromosome 7, and 3 of 5 showed trisomy of chromosome 17 by FISH, supporting classification as papillary RCC [61]. Rare cases of MTSRCC may present true sarcomatoid change a finding of importance in terms of differential diagnosis [88]. MTSRCC may be "mucin-poor" and show a marked predominance of either of its principal morphologic components, which coupled with the presence of other unusual features such as clear cells, papillations, foamy macrophages, and necrosis, may mimic other forms of renal cell carcinoma [94]. Pathologists must be aware of the spectrum of histologic findings within MTSRCC to ensure their accurate diagnosis [94-98]. Mucinous tubular and spindle cell renal carcinomas are uncommon neoplasms with distinctive morphologic features. Since MTSRCC shares several morphological characteristics with type I papillary renal cell carcinoma and its morphologic variants, knowledge of their molecular and immunohistochemical profiles can be important in distinguishing between them [12, 61- 98].

IX. RENAL CARCINOMAS ASSOCIATED WITH Xp11.2 TRANSLOCATIONS/TFE3 GENE FUSIONS

These carcinomas are defined by several different translocations involving chromosome Xp11.2, all resulting in gene fusions involving the *TFE3* gene. The first reported translocation was the t(X;1)(p11.2;q21), which results in fusion of the *PRCC* and *TFE3* genes. Another chromosome translocation is the t(X;17)(p11.2;q25), which results in fusion of the *ASPL* (a.k.a. *RCC17* or *ASPS*) and *TFE3* genes. Of note, the identical *ASPL*-*TFE3* gene fusion is also characteristic of alveolar soft part sarcoma (ASPS), where it was originally identified. Other reported translocations include a t(X;1)(p11.2;p34), resulting in fusion of the *PSF* and *TFE3* genes, and an inv(X)(p11;q12), resulting in fusion of the *NonO* (*p54^{nrb}*) and *TFE3* genes. These carcinomas predominantly affect children and young adults, though rare adult cases have been reported. The *ASPL*-*TFE3* carcinomas characteristically present at advanced stage; almost all cases have been associated with lymph node metastases at diagnosis, even with small primaries [99-106].

1. MACROSCOPIC APPEARANCE

Renal carcinomas associated with Xp11.2 translocations resemble conventional (clear cell) renal carcinomas on gross examination, most commonly being tan-yellow, and often necrotic and hemorrhagic.

2. HISTOPATHOLOGY

The most distinctive histopathological appearance is that of a papillary carcinoma comprised of clear cells; however, these tumors frequently have a more nested architecture, and often feature cells with granular eosinophilic cytoplasm. The morphologic appearance of carcinomas associated with specific chromosome translocation breakpoints differs. The *ASPL*-*TFE3* renal carcinomas are characterized by cells with a luminous clear to eosinophilic cytoplasm, discrete cell borders, a nuclear chromatin and prominent nucleoli. Psammoma bodies are constant and sometimes extensive, often arising within characteristic hyaline nodules. The *PRCC*-*TFE3* renal carcinomas generally feature less abundant cytoplasm, fewer psammoma bodies, fewer hyaline nodules, and a more nested, compact architecture. Too few *PSF*-*TFE3* and *NonO*-*TFE3* renal tumors have so far been studied to comment on their distinctive histopathological features, if any.

3. IMMUNOPROFILE

Only about 50% of renal carcinomas with Xp11.2-

associated translocations express epithelial markers such as cytokeratin and EMA by immunohistochemistry, and the labeling is often focal. Vimentin immunoreactivity is also often focal, which contrasts with conventional renal carcinomas. S-100 protein, desmin, and HMB45 are consistently negative. The tumors consistently label for the Renal Cell Carcinoma Marker antigen and CD10, similar to conventional renal carcinomas. The most distinctive immunohistochemical feature of these tumors is nuclear immunoreactivity for TFE3 protein, which is a common feature in all Xp11.2-associated carcinomas and ASPS.

4. ELECTRONMICROSCOPY

Ultrastructurally, Xp11.2-associated carcinomas most closely resemble conventional renal carcinomas because they feature cell junctions, microvilli, intracytoplasmic fat and glycogen. However, a significant number of cases demonstrate distinctive ultrastructural features. Most of the *ASPL-TFE3* renal carcinomas demonstrate membrane-bound cytoplasmic granules and a few contain membrane-bound rhomboidal crystals identical to those seen in soft tissue ASPS. Occasional *PRCC-TFE3* renal carcinomas have demonstrated distinctive intracisternal microtubules identical to those seen in extraskelatal myoid chondrosarcoma.

5. MAJOR DIFFERENTIAL DIAGNOSIS

- *Papillary renal cell carcinoma*. Translocation renal cell carcinomas sometimes often show well developed papillary structures. However, they lack the cytogenetic abnormalities that are typical of classic papillary RCC - trisomy of 7 and 17, and loss of chromosome Y.
- *Clear cell RCC*. Some translocation renal cell carcinomas exhibit the presence of clear cells forming nested architecture, and are difficult to distinguish from classic clear cell RCC; however, translocation renal cell carcinoma lacks the chromosome 3p deletion typical of clear cell RCC.

6. CYTOGENETICS AND MOLECULAR ALTERATIONS

As mentioned above, these tumors are defined by Xp11.2 translocations and resulting *TFE3* gene fusions. *TFE3* is a member of the basic-helix loop-helix family of transcription factors, while *PSF* and *NonO* encode splicing factors. *PRCC* and *ASPL* encode novel proteins for which a function has not yet been discovered, but the former may also be involved in splicing. Both the *PRCC-TFE3* and *ASPL-TFE3* fusion proteins retain the *TFE3* DNA binding domain, localize to the nucleus, and can act as aberrant transcription factors. Through interactions with other proteins, *PRCC-TFE3* may also interfere with splicing and mitotic checkpoint control. The expression levels of *TFE3* fusion proteins appear

aberrantly high compared to native *TFE3*, perhaps because the fusion partners of *TFE3* are ubiquitously expressed and contribute their promoters to the fusion proteins. In terms of structural heterogeneity, two alternative types of *ASPL-TFE3* fusion transcripts and four types of *PRCC-TFE3* transcripts have been described, but there are no apparent morphologic or clinical correlates of this genetic variability. Interestingly, while both the t(X;17) renal carcinomas and the soft tissue ASPS contain identical *ASPL-TFE3* fusion transcripts, the t(X;17) translocation is consistently balanced (reciprocal) in the former but usually unbalanced in the latter (i.e. the derivative X chromosome is not seen in ASPS).

7. PROGNOSIS

Very little is known about the clinical behavior of these carcinomas. While the *ASPL-TFE3* renal carcinomas usually present at advanced stage, their clinical course thus far appears to be indolent. Serial *PRCC-TFE3* renal carcinomas have recurred late, up to 20 or 30 years after initial diagnosis.

X. RENAL CELL CARCINOMA UNCLASSIFIED

1. MORPHOLOGICAL CRITERIA FOR PATHOLOGICAL DIAGNOSIS

In surgical series, it represents 4-7% of renal tumors [12, 107], and at presentation most are of high grade and stage at diagnosis with poor survival [12, 96, 97, 98, 107, 108, 109, 110, 111, 112]. The proportion of unclassified RCC carcinoma did not change with increasing decade of life in one study [108]. Features which might place a carcinoma in this category are defined by the current WHO classification of kidney cancer [12]. Limited reported data suggests that it is an aggressive form of RCC, mainly because most cases are at advanced stage at presentation [12, 107-110]. Results based on two relatively large series support this suggestion. Zisman et al [109] reported 31 patients with unclassified RCC and compared the prognostic outcome with 317 matched patients with clear cell RCC. The incidence of unclassified RCC in his series was 2.9% [109]. At initial diagnosis 29 patients (94%) with unclassified and 264 (83%) with clear cell RCC had metastatic disease (p = 0.143). Compared with the clear cell variety unclassified disease was associated with larger tumors (p = 0.005), increased risk of adrenal gland involvement (25% of cases, p = 0.0001), direct invasion to adjacent organs (42%, p = 0.00001), bone (52%, p = 0.022), regional lymph node (52%, p = 0.0042) and non-regional lymph node (41%, p = 0.03) metastases [109]. Unclassified histology was a significant indicator for poor prognosis on multivariate analysis (p < 0.0001) [109]. Median survival in patients with

unclassified renal cell carcinoma was 4.3 months [109]. Most recently, Karakiewicz et al [110] reviewed 85 cases of unclassified RCC to compare cancer-specific mortality in patients with unclassified RCC vs. clear cell RCC after nephrectomy. Of patients with unclassified RCC, 80% had Fuhrman grades III or IV vs. 37.8% for clear cell RCC [110]. Moreover, 36.5% of patients with unclassified RCC had pathologically confirmed nodal metastases vs. 8.6% with clear cell RCC. Finally, 54.1% of patients with unclassified RCC had distant metastases at the time of nephrectomy vs. 16.8% with clear cell RCC. Despite these differences in the overall analyses, after matching for tumor characteristics, the unclassified RCC-specific mortality rate was 1.6 times higher ($P = 0.04$) in matched analyses and 1.7 times higher ($P = 0.001$) in multivariate analyses.⁵ Both, Zisman et al [109] and Karakiewicz et al [110] concluded that unclassified RCC is associated with distinct and highly aggressive biological behavior, and poor clinical outcome.

2. RECOMMENDED PATHOLOGICAL GUIDELINES IN THESE CASES

According to the current WHO classification of kidney cancer [12, 96] the features to define unclassified RCC include: i) composites of recognized types, ii) pure sarcomatoid morphology without recognizable epithelial elements, iii) mucin production, iv) rare mixtures of epithelial and stromal elements, and v) unrecognized cell types.

Pathologic studies on unclassified RCC are very limited with most reporting on small cases series [12, 96, 97, 98, 107, 108, 109, 110, 111, 112]. Reuter [107], following the WHO criteria suggests that unclassified RCC represents a histologically and clinically heterogeneous category of tumors that does not fit neatly into any of the other well-defined categories. Bakshi et al [111] reported that RCC antigen is expressed by 85% of unclassified RCC in their series. Bruder et al [112] reported 13 cases of unclassified RCC in a series of 41 renal cell carcinomas of patients younger than 22 years. These tumors could not be assigned to types specified by the current WHO classification; of these, 10 cases were grouped as unclassified not otherwise specified, including a unique renal cell carcinoma with prominently vacuolated cytoplasm and WT1 expression. Three additional unclassified RCC occurred in combination with nephroblastoma. The study by Bruder et al [112] adds new morphologic features which together with the WHO criteria might place a carcinoma in the category of unclassified RCC. Pathologists must be aware of the spectrum of histologic findings within unclassified RCC to ensure their accurate diagnosis [12, 96, 97, 98, 107, 108, 109, 110, 111, 112].

XI. NON 2004 WHO RCC SUBTYPES CONSIDERED

1. TUBULOCYSTIC CARCINOMA

These tumours are composed by packed tubules and cysts lined by cuboidal or hobnail cells with abundant eosinophilic cytoplasm and large nuclei showing prominent nucleoli.

a) Clinical features

Tubulocystic carcinoma has been in part described as a subset of the group of the Bellini's tumour or as low-grade collecting duct carcinoma.[113] It has been reported most in adults and with a male/female ratio 7:1. Radiologically, it has a broad radiological differential diagnosis and can be classified as a Bosniak type II, III and IV. The great majority of these tumors behave in an indolent fashion, but a few have metastasized. [114-117].

b) Macroscopy

This tumour is usually a solitary unencapsulated tumor with a white or gray spongy cut surface. They can be variable in size, although most of them are pT1 tumors. Multifocal cases have been reported and association with papillary neoplasms have been provided.[114-117].

c) Histopathology

It is composed of packed tubules and cysts separated by bland fibrous stroma. The lining cells are cuboidal to columnar and hobnail cells are commonly seen. The cells have an abundant eosinophilic or amphophilic cytoplasm and the nuclei are large and have prominent nucleoli (**Fig. 13**). Occasional cells with a low-grade nuclear changes may be seen.[114-117].

The differential diagnosis include a various spectrum of tumours namely, multiloculated clear cell renal cell carcinoma, cystic nephroma, mixed epithelial and stromal tumor and cystic oncocyoma.

d) Immunoprofile

A wide range of marker positivity with cytokeratins (CK8, CK18, CK19) are consistently positive. CD10 and P504S (racemase) are positive in greater than 90% of tumors. CK7 is variable expressed, although that pattern may be weak and focal. Staining for kidney-specific cadherin and Pax-2 may also be seen. High molecular weight cytokeratin (34BE12) is nearly always negative. [114-117]

e) Somatic genetics

Gene expression profiling and fluorescence in situ hybridization studies indicate that tubulocystic carcinoma has a molecular signature consisting in gains of chromosomes 7 and 17.[114-117]

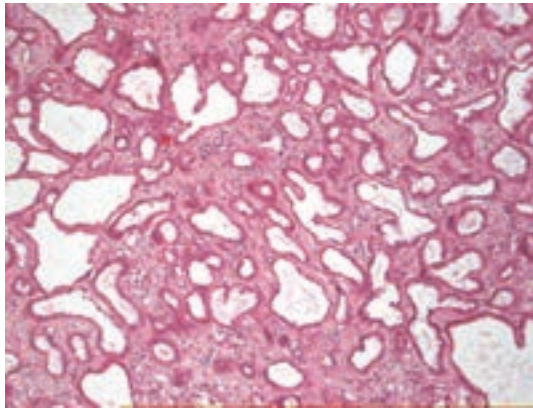


Fig. 13A.- Tubulo-cystic carcinoma.

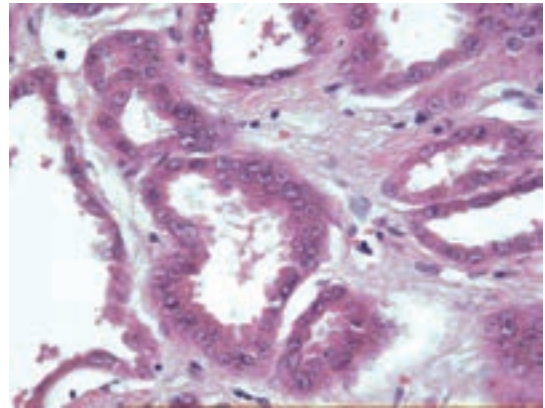


Fig. 13B.- Tubulo-cystic carcinoma.

f) Discussion

The histogenesis of tubulocystic carcinoma is unclear. The association with multiple papillary neoplasms prompted the argue that tubulocystic carcinoma may represent a subset of papillary renal cell carcinoma such as multiloculated clear cell renal cell carcinoma is considered a variant of clear cell renal cell carcinoma. Due to unique clinico-pathological and genetic characters, this type of renal cell carcinoma merit a formal recognition in a renewed future classification.

2. THYROID-LIKE (FOLLICULAR) RENAL CARCINOMA

This tumour is a renal carcinoma with a follicular architecture resembling follicular carcinoma of the thyroid and composed by cells showing low-grade pleomorphism with amphophilic to eosinophilic cytoplasm.

a) Clinical features

The seven tumors reported to date were from four female patients and three male adult patients. All tumors were incidental findings and two patients had a past history of unrelated malignancies. The tumors were tan colored and show a variable size and low pT. Follow-up data were available for all seven cases and all patients remained tumor free after 6–84 months.[118, 119].

b) Microscopy

The tumors contain a pseudocapsule and are composed of cells showing low-grade pleomorphism with amphophilic to eosinophilic cytoplasm. The cells aggregate into micro and macrofollicles. Colloid-like proteinaceous fluid may be revealed. Pseudoinclusions and nuclear grooves may be present.

The main differential diagnosis for these tumors is metastases from either a primary thyroid follicular carcinoma or thyroid carcinoma arising in a teratoma. The evaluation of TTF1 expression should always

be undertaken in tumors showing this morphology to exclude metastatic disease.[118, 119].

c) Immunoprofile

Variable expression of cytokeratin 7 and CD10 have been reported. Six of the cases were negative for RCC, WT1, vimentin, Ksp-cadherin, Pax 2, AMACR, CD56 and CD57, whereas all cases were negative for TTF1.[118, 119].

d) Somatic genetics

One case showed gains of chromosome 8q24, 12 and 16, and loss of 1p36.3 and 9q21.33,103 whereas gene expression profiling showed widespread underexpression or overexpression, particularly involving chromosomes 1, 2, 3, 5, 6, 10, 11, 16 and 17.[118, 119].

e) Discussion

This tumor cannot be considered an entity because of the few cases studied and reported.

3. ACQUIRED CYSTIC DISEASE- ASSOCIATED RENAL CELL CARCINOMA AND CLEAR CELL PAPILLARY RCC

These tumors are associated with end renal disease. The former are composed by large eosinophilic cells with a rounded nucleus and large nucleolus arranged in a variety of architectural patterns and characterized by the presence of oxalate crystals; the second by cells with clear cytoplasm and low-grade nuclear pleomorphism organized in solid, tubular and microcystic areas and frequently with a pronounced cystic component.

a) Clinical features

Studies indicate an increased prevalence of carcinoma in patients with end stage renal disease. Most of the cases present more than one tumor in a single kidney. In a detailed study of 66 tumor-bearing kidneys from patients with end-stage renal disease, a wide spectrum of renal neoplasia was noted.[120, 121].

Acquired cystic disease-associated renal cell carcinoma are present in 46% of kidneys with acquired cystic disease and clear cell papillary RCC is the second tumour described. The last can occur in kidneys both with or without acquired cystic disease.[120, 121].

Outcome data for acquired cystic disease-associated renal cell carcinoma are limited, with one death from metastatic disease 34 months following diagnosis, being reported. In two other cases regional lymph node metastases were seen.[120, 121].

No deaths from clear cell papillary renal cell carcinoma associated in patients with and without end-stage renal disease have been reported.[120, 121].

b) Macroscopy

Acquired cystic disease-associated renal cell carcinoma are usually well-circumscribed, large with dystrophic calcification. Clear cell papillary RCC frequently contain a prominent pseudocapsule and cystic feature.

c) Microscopy

Acquired cystic disease-associated renal cell carcinoma displayed a variety of architectural patterns with solid, acinar, cystic and papillary patterns being present. Irregular lumina may give the tumor a cribriform appearance. Most of reported cases the tumor appeared to arise in a cyst. The tumor cells contain eosinophilic cytoplasm with a rounded nucleus and large nucleolus. Oxalate crystals are present in the majority of tumors and also calcium aggregates.[122]

Clear cell papillary RCC show in 50% of cases a pronounced cystic component; solid, tubular and microcystic areas are also present. The tumor cells show a clear cytoplasm and a low-grade nuclear pleomorphism with nuclei situated towards the surface of the papillary tufts.[120, 121].

d) Immunoprofile

Acquired cystic disease-RCCs are positive for vimentin and AMACR on immunohistochemical examination, and in a proportion of cases show variable focal staining for cytokeratin 7 and parvalbumin, discordant positive immunoperoxidation for cytokeratin AE1/AE3 and CD10, and variable expression for vimentin CAM 5.2. [123, 124].

Clear cell papillary RCC show positive staining for cytokeratin 7 and are negative for AMACR and parvalbumin.[123].

e) Somatic genetics

In a kidney showing acquired cystic disease, genetic analysis showed gains of chromosomes 7 and 17. In acquired cystic disease-RCCs FISH and

CGH analyses showed multiple gains of numerous chromosomes including chromosomes 1, 2, 6, 10, 3, 7, 17 and Y. Mutations of the VHL gene have not yet been identified in these tumors. Clear cell papillary RCC did not show neither 3p nor trisomies of chromosomes 7 and 17.[121, 124].

f) Discussion

Discrete clinico-pathological informations are present in regard to acquired cystic disease-RCCs whereas more data are needed for the clear cell papillary RCC and its possible relationship with other.

4. LEIOMYOMATOUS RENAL CELL CARCINOMAS

They are tumors composed of tubular aggregates of neoplastic clear cell intermingled in a prominent leiomyomatous proliferation.

a) Clinical features

Among 12 reported cases, eight female and four male patients ranged in adult ages. Two of the patients had co-existing cancer (breast carcinoma and papillary renal cell carcinoma) and one patient had tuberous sclerosis. Most tumors were incidental findings, although three patients presented with hematuria. Outcome studies for leiomyomatous renal cell carcinoma are limited. No evidence of recurrence or metastases was seen in these and two other cases followed from 6 months to 5 years (mean 3 years). [74, 125, 126].

b) Macroscopy

Grossly the tumors measured 1.8–14 cm (mean 4.6 cm) and were variously described as tan, brown, yellow or white with the frequent presence of a thick investing capsule. Of cases for which details are available, four were pT1a and one pT1b at diagnosis.

c) Microscopy

The tumors are composed of nests, cords and sheets of epithelial cells frequently forming solid areas, tubules or papillary structures. There is slight nuclear pleomorphism with abundant clear cytoplasm. The stroma is composed by mature smooth muscle which is often more pronounced at the periphery and in some cases appears to extend into adjacent renal tissue or into perirenal fat.

The differential diagnosis for these tumors is clear cell renal cell carcinoma, angiolipoma and sarcomatoid renal cell carcinoma. [74, 125, 126].

d) Immunoprofile

The epithelial component of the tumor showed positive immunoperoxidation of cytokeratins AE1/AE3 and CAM 5.2, CD-10, S-100 protein (focal), EMA and vimentin. There was variable expression of 34bE12, whereas smooth muscle actin and HMB45 was

negative. The stroma component was positive for a smooth muscle actin, caldesmon, desmin, vimentin and negative for HMB45, CD117, cytokeratins, EMA, ER and PR.[74].

e) Somatic genetics

Genetic studies on these tumors are contradictory. In three cases FISH showed loss of VHL and FHIT, with loss of chromosome 3 in one case and 3p in another. In a separate study there was no evidence of 3p deletion in the three cases examined.[74].

There is still a debate among the relationship between the renal adenomatous tumour (RAT) recently described [127], clear cell papillary and leiomyomatous renal cell carcinoma. Microscopically, examination reveals a leiomyomatous stroma surrounding and encasing a distinctive and characteristic epithelial component. This latter is represented by adenomatous structures composed of cells with small deeply basophilic nuclei alienated along the basal membrane. Along these characters, clear cell papillary renal carcinoma may also show overlapping morphological features. Finally all these neoplasms are constantly positive for CK7. Due to aforementioned morphological contrasting findings, a formal classification is early.

XII. CRITICAL REVIEW OF GRADING

At first the Fuhrman's grade was applied only to the clear cell renal cell carcinomas. Nowadays the grading of all cell subtypes is recommended. But in non clear cell types some criticism appears in the use of this system, for this reason we will consider the grading in different histological subtypes.

1. CLEAR CELL RENAL CELL CARCINOMA

Despite criticisms to the reproducibility of the Fuhrman's nuclear grade (based on the size and shape of the nucleus and also on the presence or absence of nucleoli) [128] it is the most widely method used internationally.

It is a good prognostic marker with, a 5-year cancer specific survival rate of 89%, 65% and 46% for grades 1, 2 and 3-4, respectively [129]. The present trend is to subdivide the four Fuhrman's grades into low grade (grade 1 and 2) and high grade (grade 3 and 4) [130]. With this approach the interobserver and intraobserver reliability is improved without loss of outcome discrimination [131].

The wider use of ultrasound favours the detection of asymptomatic renal tumours [132] with a higher incidence of organ-confined carcinomas. In this situation the Fuhrman's grading can also be of help. Nuclear grade greater than 2 correlates with significantly shorter survival ($p = 0.018$) in Stage I tumours [133].

2. PAPILLARY RENAL CELL CARCINOMA

The study of the different criteria of Fuhrman's system only focal nucleolar grade was associated with survival, on univariate and multivariate analysis in papillary RCC [134]. That means that the nucleolar size is, probably, most important that the subtype.

3. CHROMOPHOBE RCC

Irregular nuclei and prominent nucleoli are typically seen. Therefore, Fuhrman's grade is often reported worse even in patients with favorable outcomes. Some authors propose an adaptation of the classification for this RCC subtype with redefinition of three grades for chromophobe RCC: Grade 1: cells with wide nuclear range without nuclear crowding or anaplasia. Grade2: presence of nuclear pleomorphism and nuclear crowding. Grade 3: nuclear anaplasia including giant cells and sarcomatoid transformation. This new system accepts the more pleomorphic nuclear aspect in low grades that correlates better with the pT category and predicts the clinical outcome independently [135] This new approach should however be validated by other series before its introduction in clinical practice.

Finally, the *Mucinous tubular and spindle cell carcinoma*, a new subtype in the WHO 2004 classification, is not graded. Likewise, the *Oncocytoma*, as a benign tumor, is not graded.

XIII. GUIDELINES FOR PATHOLOGICAL STAGING EVALUATION

The quality of any pathological evaluation depends on a careful macroscopic examination of the surgical specimens [136]. Basic for an efficacious pathological study are: identification of the anatomical structures, preservation of the complete specimens (i.e. no cuts), and appropriate handling by urologists.

The specimens should be manipulated when fresh. Avoid stripping the capsule before sectioning the specimen, and identify the renal vein, the renal artery, and the ureter. Careful external inspection is basic for evaluating the radicality of the nephrectomy. The areas where such radicality is dubious should be inked with Indian ink before sectioning.

The specimen should be sectioned every 10 mm including the perinephric fat tissue. Every tumoral nodule and anatomical structure should be identified and the specimen should be fixed and left overnight.

Samples for microscopy study should be selected and identified by means of identification labels, and they should include: i) One tumour section per every centimetre of tumour diameter. ii) Section of the tumour-fat tissue interface. iii) Accurate study of the

sinus fat tissue close to the tumour, with a sagittal section of this area [137] *inclusion of the sinus fat tissue* seems to entail greater aggressiveness (5 years specific survival 25.9%) than perinephric fat tissue invasion (5 years specific survival 50.9%) [138], probably because it contains a number of large thin-walled veins and lymphatics, and it is not separated from the renal cortex by a fibrous capsule [139] *iv*

Section of the renal vein, even if normal. *v* Two or three samples of normal kidney, close to the tumour and also distal to it. One of the objectives of this sampling is finding microvascular invasion. *iv*) Adrenal gland section, even if the tumour is far from it. *iv*) Complete dissection including lymph nodes. The number of lymph nodes to be dissected depends on the pathologist's motivation and the urologist's skills. Generally the lymph nodes are rarely identifiable unless specifically dissected by the surgeon. In this case inclusion of the complete hilar fat tissue is recommended [137]

Margins are of the utmost importance. Positive margins are very rarely found in specimens from a radical procedure. If positive margins were found, their location and their extension should be reported.

The margins of a nephron-sparing nephrectomy are the renal parenchyma margin and the perinephric fat margin. It is advisable to ink the excision margins before dissection. The urinary tract wall should be considered a margin if the tumour extends into the calyceal system [140].

XIV. MOLECULAR BASIS OF RENAL CANCER TREATMENT

The knowledge of the molecular basis of RCC has been improved with the introduction of DNA expression analysis. Array based expression profiling allows for a molecular classification of tumours. The first gene expression profiling study in RCC was published in 2001 by Young *et al.* [141]. They analysed a total of seven samples consisting of clear cell RCC, chromophobe RCC and oncocytoma with matching normal renal tissue and found distinct differences in genes expression between these entities. Clear cell RCC could be distinguished from chromophobe RCC/oncocytoma by expression of Vimentin, whereas galectin-3 expression was more prevalent in oncocytoma/chromophobe RCC. Tachibashi *et al.* published a correlation of RCC expression profiles with clinical follow up data and defined a group of transcripts, which predicted patient risk of progression more accurately than conventional tumour staging in a small tumour cohort (n=29)[142]. Candidate diagnostic markers were identified by the same group in a larger

study (n=70): glutathione S-transferase was highly expressed in clear cell RCC, α -methylacyl racemase (AMACR) was typical of papillary RCC and carbonic anhydrase II was found in chromophobe RCC [143]. The studies of Vasselli *et al.* (58 tumors) and Jones *et al.* (49 RCCs) focused on a cluster or signature based prediction of patient prognosis [144, 145].

Our refined understanding of the molecular pathways involved in renal carcinogenesis has provided a rationale for novel therapeutics which specifically target molecules of aberrantly activated pathways. The Von Hippel-Lindau (VHL) tumour suppressor gene is epigenetically silenced or mutated in the majority of sporadic clear cell renal carcinoma (see above). The decreased pVHL expression leads to a stabilisation of the hypoxia induced factor (HIF)- α and consequently to the transcription of HIF- α target genes, many of which are involved in tumour promoting processes as proliferation, angiogenesis and cell motility [148]. Targeting the transcription factor HIF directly is difficult, but a variety of agents have been identified that downregulate HIF- α levels indirectly, e.g., inhibitors targeting the mammalian target of rapamycin (mTOR) [149, 159] or Heat shock protein 90 (HSP90) [149, 150]. Another approach is to target HIF- α regulated genes directly. HIF- α responsive genes of major importance in tumour biology are VEGF, PDGF, TGF α , EGFR and Ca IX. **VEGF** is overexpressed in RCC and has prognostic properties [151]. **PDGF** (Platelet-derived growth factor) correlates to higher Fuhrman grades and appears to be a prognostic marker in RCC [152]. **TGF (Transforming growth factor)**. TGF- α is overexpressed in RCC and is induced by hypoxia [153]. TGF- β is overexpressed in various malignant tumors including RCC [154]. **EGFR (Epidermal growth factor receptor, ErbB-1)** is overexpressed in the majority of RCC [155, 156]. **CA IX (Carbonic anhydrase IX)** is overexpressed in > 90% of clear cell RCC, but is usually not found in normal tubulus epithelium. Interestingly, in RCC it has been found as a negative marker of prognosis and is discussed as a predictive marker of IL-2 therapy response [157, 158]. Other target genes not associated with HIF- α are KIT, COX-2 and Matrix Metalloproteinases (MMP). **KIT** is a type III tyrosine kinase receptor that is overexpressed in chromophobe RCC and oncocytoma, but rarely in clear cell RCC [160]. **COX-2** is upregulated in many malignant tumours including RCC. Possibly, COX-2 is a predictive marker for therapy response to COX-inhibitors in RCC [161]. **Matrix Metalloproteinases (MMP)** have been associated with a poor prognosis in RCC [162]. A summary of relevant biomarkers in RCC has been recently published by Eichelberg *et al.* (Eichelberg C, Junker K, Ljungberg B, Moch H. Diagnostic and prognostic molecular markers for renal cell carcinoma: a critical appraisal of the current state of research and clinical applicability. [164].

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Prognostic Factors of Renal Cell Carcinoma: A contemporary Review

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Prognostic Factors of Renal Cell Carcinoma: A contemporary Review

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I. INTRODUCTION

The natural history of renal cell carcinoma (RCC) may be unpredictable. For example, between 4.2 and 7.1% of patients with tumors ≤ 4 centimeters that are usually indolent in nature, harbor metastatic disease at presentation and are at an elevated risk of disease-specific mortality. [1] Conversely, as many as 40% of patients with lymph node metastases diagnosed at nephrectomy are alive at five years after surgery. [2] Several approaches have been proposed to help predicting the natural history of treated RCC and to distinguish between poor and favorable risk patients. In the current manuscript, we will briefly address the history of prognostics. We will review the existing prognostic factors, as well as factors predicting response to targeted therapy and complete the review with established prognostic models.

II. HISTORY OF PROGNOSTICS IN RCC

In 1988, Elson et al. pioneered the approach to multivariable modeling in prediction of cancer-specific mortality (Table 1). [3] In 1999, Motzer et al. (n=670) identified five predictors (Karnofsky Performance Status) (KPS), lactate dehydrogenase, hemoglobin, corrected calcium, and presence/absence of nephrectomy) of metastatic RCC mortality. [4] The developed Motzer score stratified patients between favorable (0 risk factors), intermediate (1-2 risk factors), and poor risk (≥ 3 risk factors). [4] In 2002, an update of the Motzer score (n=463) replaced nephrectomy status with time from diagnosis to start of interferon. [5] In 2004, a second update (n=251) reduced the score to three predictors (KPS, hemoglobin, and corrected calcium). [6]

In 2005, Makhail et al. suggested several modifications to the 2002 Motzer score variables (KPS, lactate dehydrogenase, hemoglobin, corrected calcium, and time from diagnosis to start of interferon) [5] such as addition of previous exposure to radiotherapy and variables indicating the presence of nodal, hepatic, and/or lung metastases (n=353; Table 1). [7] In 2007, Escudier et al. also suggested the replacement of KPS with the number of metastatic sites. [8] Unfortunately, none of the original Motzer models were formally validated. In consequence, their accuracy, performance characteristics and impact on clinical decision-making remain unknown.

A report from the *Groupe Français d'Immunothérapie* suggested a different prognostic model, which identified four variables that were statistically significantly associated with progression in patients receiving immunotherapy (Table 1). These consisted of time from RCC diagnosis to metastases, number of metastatic sites, presence of hepatic metastases, and of the neutrophil count. [9] Recently, Heng et al. [10] devised and internally validated a model that replicates the Motzer methodology and relies on four of five Motzer criteria (hemoglobin, corrected calcium, KPS and time from diagnosis to treatment), in addition to neutrophil and platelet counts. Of all models, the Heng et al. [10] model was the only one subjected to internal (bootstrap) validation, which showed 73% accuracy in prediction of mortality after therapy with a vascular endothelial growth factor (VEGF) therapy. It awaits its external validation.

The Motzer, Makhail, *Groupe Français d'Immunothérapie* and Heng models exclusively apply to patients with metastatic RCC. Other models have been developed for patients with all stages or non-metastatic RCC. For example, investigators from University of California Los Angeles (UCLA) devised an integrated staging system (UISS) for prediction of survival in patients with all stages of RCC

Table 1. Prediction of overall survival and/or progression-free survival in metastatic renal cell carcinoma

Model	Sample size	Target population	Predictors	c-index
Elson et al. [3]	610	mRCC	- ECOG-PS - time from initial diagnosis - Number of metastatic sites - prior cytotoxic chemotherapy - weight loss	n.r.
Motzer et al. [4]	670	mRCC treated with NT	- lactate dehydrogenase >ULN - hemoglobin >ULN - KPS - corrected serum calcium >ULN - absence of NT	n.r.
Motzer et al. [5]	463	mRCC treated with NT/INF	- KPS - lactate dehydrogenase <ULN - hemoglobin >ULN - corrected serum calcium >ULN - time from diagnosis to IFN	n.r.
Motzer et al. [6]	251	mRCC treated with NT/INF	- KPS - hemoglobin >ULN - corrected serum calcium >ULN	n.r.
Negrier et al. [147]	782	mRCC treated with cytotoxic	- presence of biological signs of inflammation - short time interval from renal tumor to mRCC - elevated neutrophil count - liver metastases - bone metastases - performance status - number of metastatic sites - alkaline phosphatase - hemoglobin	n.r. (OS)
Negrier et al. [147]	782	mRCC treated with cytotoxic	- presence of hepatic metastases - short interval from renal tumor to metastases - ≥1 metastatic site - elevated neutrophil count	n.r. (PFS)
Leibovich et al. [152]	173	mRCC treated with NT/IL-2	- N classification - constitutional symptoms - location of metastatic sites - histological subtype - sarcomatoid features - thyroid stimulating hormone levels	n.r.
Leibovich et al. [126]	727	metastatic clear cell RCC treated with NT	- age - gender - symptoms at NT - time from NT to mRCC - location/surgical treatment of metastases - presence/level of tumor thrombus - histological subtype - TNM (2002) - tumor size - perinephritic fat invasion - lymph node invasion - nuclear grade - tumor necrosis - sarcomatoid differentiation	67.0%

Table 1. Prediction of overall survival and/or progression-free survival in metastatic renal cell carcinoma (continued)

Negrier et al. [9]	782	mRCC patients treated with cytokine	<ul style="list-style-type: none"> - ≥ 1 metastatic site - having received combination of therapies 	n.r. (efficacy)
Mekhail et al. [7]	353	mRCC	<ul style="list-style-type: none"> - multifocality - time from diagnosis to study entry - lactate dehydrogenase >ULN - corrected serum calcium >ULN - previous radiotherapy - presence of hepatic/pulmonary/retroperitoneal/lymph node metastases 	n.r.
Donskov et al. [184]	120	mRCC patients treated with IL-2	<ul style="list-style-type: none"> - lactate dehydrogenase - lymph node metastases - hemoglobin - KPS - bone metastases - high blood neutrophil count - presence of intratumoral neutrophils - low intratumoral CD57+ natural killer cell count 	n.r.
Choueiri et al. [183]	120	mRCC patients treated with VEGF agents	<ul style="list-style-type: none"> - corrected serum calcium >ULN - neutrophil count >ULN - platelet count >ULN - ECOG-PS - time from diagnosis to study start 	n.r.
Escudier et al. [8]	300	mRCC patients who failed immunotherapy	<ul style="list-style-type: none"> - alkaline phosphatase >ULN - corrected serum calcium >ULN - lactate dehydrogenase >ULN - number of metastatic sites - time from diagnosis to metastatic diagnosis 	n.r.
Motzer et al. [185]	375	mRCC patients treated with sunitinib	<ul style="list-style-type: none"> - corrected serum calcium - number of metastatic sites - hemoglobin >ULN - prior NT - lung metastases - liver metastases - ECOG-PS - thrombocytopenia - time from diagnosis to treatment - alkaline phosphatase - lactate dehydrogenase 	63.0%
Heng et al. [10]	645	mRCC patients treated with VEGF agents	<ul style="list-style-type: none"> - KPS - time from diagnosis to treatment - hemoglobin >ULN - corrected serum calcium >ULN - neutrophil >ULN - platelet >ULN 	73.0%

Legend: mRCC: metastatic renal cell carcinoma; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; NT: nephrectomy; ULN: upper limit normal; KPS: Karnofsky performance status; INF: interferon; OS: overall survival; PFS: progression-free survival; IL-2: interleukin-2; VEGF: vascular endothelial growth factor; n.r.: not reported

(Table 2). [11, 12] This model relies on the TNM stage, Fuhrman grade, and ECOG-PS and has been widely tested and validated (c-indices: 58-86%). [13-19] A multi-institutional collaborative group of European and North American investigators developed two prognostic models that address RCC-specific mortality based on variables that can be obtained either prior (**Table 3**) to or after nephrectomy (**Table 4**). These two models can predict the natural history of RCC after nephrectomy. However, they are not designed to account for the effect of targeted therapies in patients with metastatic RCC. [20, 21]

The accuracy of the pre-nephrectomy model for prediction of cancer-specific mortality at 5 years is 86.7% vs. 86.8% for the post-nephrectomy model (**Table 2**). Similar models were developed by other investigators and allow estimation of recurrence-free survival [22, 23] or metastatic progression after nephrectomy, [24] with accuracy rates between 65 and 80%. Multivariable models such as the UISS [11], the Kattan postoperative nomogram [25], BioScore [26], and SSIGN score (tumor stage, size, grade, necrosis) [27] have better prognostic ability than anatomical staging alone (**Table 4**). Despite their

Table 2. Postoperative assessment of cancer-specific mortality

Model	Sample size	Target population	Predictors	c-index
Zisman et al. [11]	661	RCC of all stages	- AJCC - Fuhrman grade - ECOG-PS	82.0-86.0%
Zisman et al. [12]	814	RCC of all stages	- TNM (1997) + ECOG-PS	73.0% 79.0-86.0%
Frank et al. [27]	1801	Localized clear cell RCC	- TNM (1997) - tumor size - nuclear grade - tumor necrosis	85.0% (int.) 81.0-82.0% (val.)
Kim et al. [97]	318	RCC of all stages	- M stage - metastatic CAIX - p53 - imatinib - geldanerin	79.0%
Kim et al. [182]	150	Metastatic clear cell RCC	- T stage - ECOG-PS - CAIX - imatinib - p53 - PTEN	68.0%
Thompson et al. [187]	1560	Localized clear cell RCC	- TNM (1997) - tumor size - nuclear grade - tumor necrosis	n.r.
Karakiewicz et al. [20]	2530 (dev.) 1422 (val.)	Clear cell, papillary, chromophobe RCC	- pT stage - pN stage - M stage - tumor size - Fuhrman grade - Symptoms classification	87.8-89.2% (val.)
Karakiewicz et al. [188]	2530 (dev.) 3560 (val.)	RCC of all stages	- pT stage - pN stage - M stage - tumor size - Fuhrman grade - Symptoms classification	87.0-91.0% (val.)
Parker et al. [26]	818	Clear cell RCC	- B7-H1 - survival - Ki-67	73.3%

Legend: RCC: renal cell carcinoma; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; int.: internal; val.: validation; dev.: development

Table 3. Preoperative assessment of prognosis

Model	Sample size	Outcome	c-index
Yaycioglu et al. [23]	296	Recurrence after nephrectomy	65.1%
Cindolo et al. [22]	660	Recurrence after nephrectomy	67.2%
Raj et al. [187]	290 (dev.) 94 (val.)	Clear cell RCC	82% (dev.) 76% (val.)
Lane et al. [188]	851	Benign vs. malignant Indolent vs. aggressive	64.4% 55.7%
Hollingsworth et al. [189]	26618	CSM and OS	n.r.
Hutterer et al. [190]	2522 (dev.) 2136 (val.)	Lymph node metastases at nephrectomy	78.4%
Raj et al. [24]	2517	Metastatic recurrence after nephrectomy	80.0%
Karakiewicz et al. [21]	2474 (dev.) 1972 (val.)	CSM	84-88%
Hutterer et al. [191]	2660 (dev.) 2716 (val.)	Distant metastases at nephrectomy	85.0%
Kutikov et al. [192]	30801	CSM, OCM, NCM	n.r.

Legend: dev.: development; val.: validation; n.r.: not reported; CSM: cancer-specific mortality; OCM: other-cancer mortality; NCM: non-cancer related mortality; OS: overall survival; RCC: renal cell carcinoma

Table 4. Postoperative assessment of recurrence

Model	Sample size	Target population	Predictors	c-index
Kattan et al. [25]	601	Localized RCC	- symptom classification - histological subtype - tumor size - pT stage	74.0% (overall rec.)
Frank et al. [193]	1864	Localized clear cell RCC	- age - gender - symptom classification - TNM (1997) - nuclear grade - tumor necrosis - sarcomatoid feature - cystic architecture - multifocality - surgical margin status - nephrectomy type	80.5% (abdominal rec.) 82.6% (thoracic rec.) 80.0% (bone rec.)
Sorbellini et al. [194]	701	Localized clear cell RCC	- symptom classification - tumor size - pT stage - Fuhrman grade - tumor necrosis - nuclear invasion	82.0% (overall rec.)
Lam et al. [195]	559	Localized/locally advanced RCC	- TNM (1997) - nuclear grade - ECOG-PS	n.r. (solitary rec., chest rec., abdominal rec., bone rec., brain rec.)

Legend: RCC: renal cell carcinoma; rec.: recurrence; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; n.r.: not reported

adequate prognostic ability, none of these models is 100% accurate. In consequence, the search for more accurate markers continues. Molecular events that can unveil the biological heterogeneity underlying the varied clinical behavior of RCC may help in improving individualized prognostication and risk-stratified clinical decision-making. The hope and interest lies in the identification of accurate markers that will predict the responses to the existing effective but toxic systemic therapies [28-32].

Over the past two decades, the molecular dissection of cancer has increased our understanding of the pathways that are altered in neoplastic cells. While some biomarkers were shown to be associated with other established clinical and/or pathological characteristics of RCC (Table 5), others demonstrated a meaningful effect with progression-free survival, overall survival, cancer-specific mortality, prognosis, and even added value when incorporated with existing prognostic models (Table 6). The following paragraphs will outline the existing biomarkers, which demonstrated a potential for improving the predictive and/or prognostic ability of clinical and pathologic variables.

III. RCC BIOMARKERS

1. TISSUE-BASED BIOMARKERS

a) *Von-Hippel-Lindau (VHL) gene*

The VHL gene was originally described, isolated, and identified as a tumor suppressor gene on chromosome 3p resulting in deficient protein isoforms pVHL19 and pVHL30 (Fig. 1). Its absence in the VHL familial tumor syndrome predisposes to retinal angiomas, central nervous system hemangioblastomas, pancreatic tumors, pheochromocytomas and multiple bilateral clear cell RCC lesions. [33] VHL is inactivated in almost all patients with VHL syndrome and approximately 70% of sporadic clear cell RCC. [34] Alteration in the VHL proteins results in impaired degradation of hypoxia-induced factor 1- α (HIF-1 α), which accumulates even under normal (non-hypoxic) conditions. Other VHL gene effects include regulation of the cell-cycle arrest via p53 and deposition of extracellular matrix.

Presence of VHL alterations (mutation or hypermethylation) predicts longer progression-free survival and lower mortality for stage I-III clear cell RCC ($p=0.024$ and 0.023 , respectively). [34] However, the survival rate of patients with VHL mutations was not different from patients without VHL mutations in other analyses. [35] The investigators postulated that regulation of angiogenesis and proliferation of RCC is not directly influenced by VHL mutations, but that "loss-of-function" VHL mutations directly influence the progression of RCC.

Rini et al. showed that 60% of metastatic RCC patients had VHL mutations and that 48% of those patients achieved an objective response to targeted therapy. 35% for patients with no VHL mutation or methylation. [36] The independent prognostic effect of VHL mutation was also reported even after adjusting for ECOG-PS, hemoglobin, corrected calcium, lactate dehydrogenase, radiation exposure, previous therapy and number of metastatic sites. [37] In pazopanib-treated patients, a 76% clinical benefit rate (partial response+stable disease) was achieved in patients with VHL gene mutation. 63% in those without. [38] Similar findings were recorded, where loss-of-function VHL mutation conferred a 52% response rate (partial response+complete response) to targeted therapies. 31% for wild-type VHL ($p=0.04$). [39] Additional studies are clearly needed to better elucidate the role of VHL mutations in sporadic RCC, especially in the context of targeted therapies. However, added data quantifying the added benefit and externally validated accuracy results of models that integrate VHL are not yet available.

b) *Hypoxia Inducible Factor (HIF- α)*

HIF- α accumulates either in hypoxic cell conditions or when pVHL is deficient (Fig. 1). Increased expression of HIF- α was recorded in 75% (24/32) of clear cell RCC and only 38% (3/8) of non-clear cell RCC cases. [40] None of the HIF-1 α -negative clear cell RCC patients showed a mutation of the VHL gene. The level of HIF- α appeared to correlate with the presence of VHL mutation. Lidgren et al. showed that clear cell RCC variant had significantly higher HIF-1 α expression compared to papillary or chromophobe RCC variants. [41] Prognostic significance of HIF- α levels was recorded only in patients with clear cell RCC ($p=0.02$; Fig. 2A), but not in patients with papillary RCC ($p=0.2$). [41]

The same authors reported no survival difference between patients with high and low HIF-1 α expression in either clear cell or papillary RCC variants (all $p \geq 0.1$). [42] Conversely, Klatte et al. showed worse survival (13.5 vs. 24.4 months, $p=0.005$) with elevated HIF-1 α tumor tissue levels (Fig. 2B). Methodological and analytical differences may account for the different findings. [43]

In patients exposed to sunitinib, high levels of HIF-1 α ($p=0.003$) or of HIF-2 α ($p=0.001$) confer more favorable response (defined as complete or partial response) to therapy. [44] Clearly, standardized methodology and more studies are needed to better understand the prognostic and predictive role of HIF- α . Added value and external validity data are awaited.

Vascular endothelial growth factor (VEGF)

VEGF, a dimeric glycoprotein and a member of the platelet-derived growth factor, affects tumor

Table 5. Molecular marker and its association with other established clinical and/or pathological characteristics of renal cell carcinoma (RCC).

Marker	Histology	Tumor stage	Tumor size	Tumor necrosis	Tumor grade	Metastatic disease/ progression	Other
Neutrophil							
C-reactive protein						+	
VHL						+	
HIF- α	+ (clear cell)						
Tissue-based							
VEGF	+/ns (papillary)	+	+	+	+		Predictor of microvessel invasion
CAIX				ns	ns	+	
mTOR							
pS6						+	
PTEN		+					
pAkt					+		+
Other							
Cadherin-1	+ (clear cell)						
p53	+ (papillary)					+	
Ki-67							
Survivin	+ (all HS)				+		Predictor of aggressive disease
B7-H1						+	
Vimentin	+ (clear cell/ papillary)						
Fascin	+ (sarcomatoid)	+	+			+	
MMP	+ (non clear cell)				+		Predictor of aggressive disease
IMP3	+ (sarcomatoid)	+		+		+	Predictor of lymph node involvement
Blood-based							
VEGF							
CAIX	+ (clear cell)	+/ns	+		ns		
NGAL							
SAA						+	
IGF-I							
NMP-22							Predictor of RCC diagnosis

Legend: +: associated with; ns: not significant

Table 6. Molecular marker and its association with progression-free survival (PFS), overall survival (OS), cancer-specific mortality (CSM), prognosis, treatment efficacy and its added value in established risk stratification for renal cell carcinoma (RCC).

Marker	Prognosis	PFS	OS	CSM	Treatment efficacy	Added value in prognostic models
Neutrophil		+	+ (in IL-2 patients)	+	ns (low response rate in IL-2 patients)	+ (Leibovich)
C-reactive protein			+			+
VHL		+/ns	+/ns	+	+ (predicts response to targeted therapy)	+
HIF- α			+		+ (predicts response to sunitinib)	
Tissue-based						
VEGF		+		+		
CAIX	+					+
mTOR						
pS6			+		+ (predicts response to temsirolimus)	
PTEN			+		+ (predicts response to mTOR inhibitors)/ ns (low response in temsirolimus)	
pAkt	+ (for localized and metastatic RCC)			+	+ (predicts response to temsirolimus)	
Other						
Caveolin-1			+/ns (coexpression with Akt/mTOR)			
p53			ns			
Ki-67		+	+	+ (coexpression with CAIX)		
Survivin		+	+			
B7-H1			+	+		
Vimentin	+					
Fascin						
MMP			+			
IMP3		+		+		+ (SSIGN)
Blood-based						
VEGF		+/ns	+/ns (in metastatic RCC)/+ (in sorafenib patients)		+ (predicts response rate in sunitinib)/ns (does not predict response rate in sorafenib)	
CAIX		+		+		
NGAL		+				
SAA			+			
IGF-I			+			
NMP-22						

Legend: +: association; ns: not significant

angiogenesis in both normal and pathologic conditions (**Fig. 1**). In tumors, angiogenesis is induced by VEGF. In clear cell RCC, the upregulation of VEGF mRNA is expected due to the dysregulation of HIF-1 α as a result of the loss of VHL protein in addition to the hypoxic environment. Larger tumors have inadequate blood supply and exacerbate hypoxia causing further upregulation of VEGF expression. Enhanced VEGF concentration correlates with VHL gene inactivation. [45, 46] Increased VEGF production occurs in RCC patients with VHL gene alterations ($p < 0.001$) and advanced grade ($p < 0.001$). [47] Elevated VEGF expression was reported in 29% of patients with clear cell RCC and unexpectedly in 67% of patients with papillary RCC ($p = 0.02$) [48], but could not be confirmed in other studies [49]. In clear cell RCC, VEGF expression correlates with tumor size ($p = 0.05$) [48], Fuhrman grade ($p = 0.002$), tumor necrosis ($p = 0.001$), tumor stage ($p = 0.006$) [50], microvessel invasion ($p = 0.01$) [51], RCC progression rate ($p = 0.01$) [50], and RCC-specific survival (**Fig. 3**). [48-50] Further confirmatory studies are needed to assess VEGF pathway with downstream molecules such as phospho-extracellular signal-regulated kinase (pERK) possibly serving as biomarker for therapy response. Despite its promising characteristics, VEGF awaits confirmation of its added value and external validity.

c) Carbonic Anhydrase IX (CAIX)

CAIX is a HIF-1 α regulated transmembrane protein associated with neoplastic growth, aggressive tumor phenotype, and poor prognosis in a large spectrum of human tumors (**Fig. 1**). [52-55] CAIX is thought to assist in regulating intra-cellular and extracellular pH levels in response to tumoral hypoxia and subsequent anaerobic metabolism. In RCC, especially clear cell RCC, CAIX can establish the diagnosis as it is expressed in over 80% of RCC samples and 90% of clear cell RCC specimens. Interestingly, high CAIX expression is associated with better prognosis in localized RCC and metastatic RCC. [56-60]

For example, CAIX staining levels have been shown to be inversely related to metastatic spread ($p = 0.036$) and high CAIX expression predicted better survival (**Fig. 4**), even after adjusting for the effects of T stage, Fuhrman grade, nodal status, and performance status (all $p \leq 0.005$). [57] Moreover, low CAIX staining ($\leq 85\%$) predicted worse outcome in patients with metastatic RCC (HR: 3.10, $p < 0.001$) [57] and even after adjustment for the effects of clinical and pathologic characteristics (HR: 4.76, $p < 0.001$) [56]. Similar findings were reported in patients who received interleukin-2 therapy ($p = 0.04$). [60] However, low CAIX expression was not associated

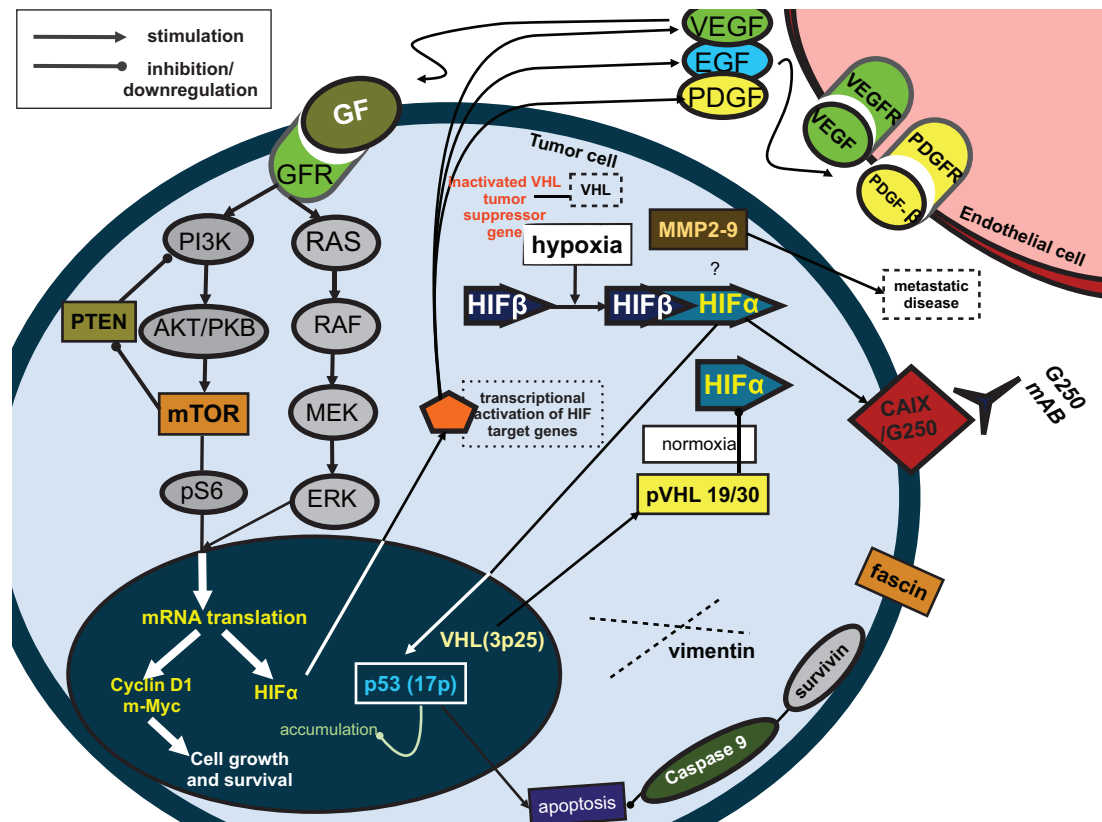


Figure 1. Biological pathways and markers in renal cell carcinoma.

with RCC death after adjusting for the effect of tumor grade ($p=0.3$) or coagulative tumor necrosis ($p=0.1$). [61] Data from ongoing trials will hopefully provide better insight in this highly promising marker. [62, 63] Besides prognostic value, the tumor-specific and high prevalence of CAIX in RCC makes it a great target for imaging and therapy using monoclonal antibodies such as G250.

d) Mammalian target of rapamycin (mTOR)

The mTOR pathway regulates cell growth and its up-regulation in tumors contributes to many critical

cellular functions such as protein degradation and angiogenesis (**Fig. 1**). [64] The prognostic role of mTOR as a biomarker is sparse and non-conclusive. However, mTOR inhibitors (temsirolimus[31], everolimus[32]) have come to represent agents of choice for metastatic RCC. The prognostic and predictive relevance of mTOR and its upstream (i.e., PTEN) and downstream (i.e., phosphorylated S6 ribosomal protein- see below) molecules are being critically evaluated to identify responders to these agents.

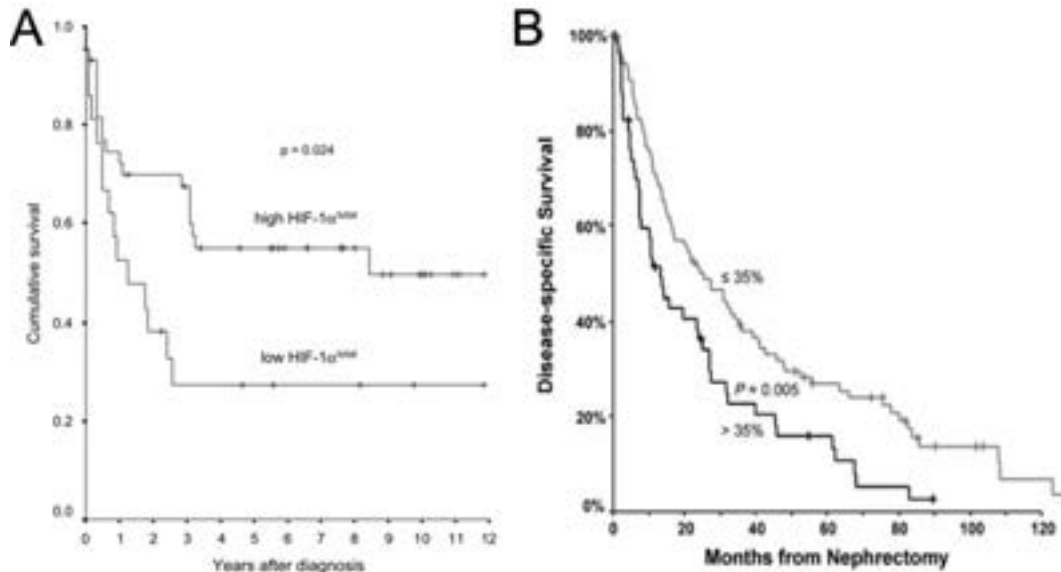


Figure 2. Kaplan-Meier survival curves stratified according to high vs. low HIF-1 α levels in patients with clear cell renal cell carcinoma [41, 43]

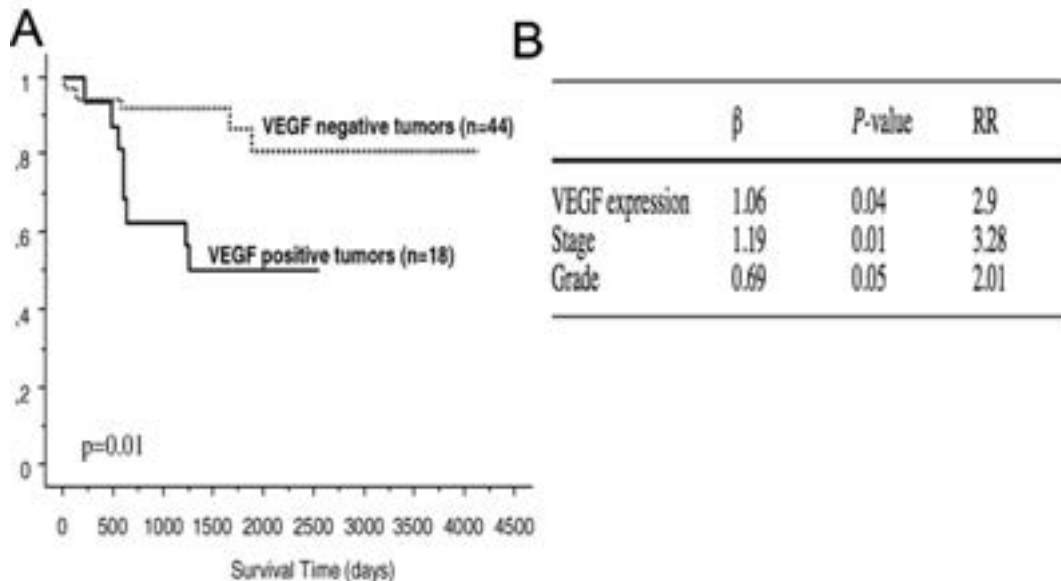


Figure 3. Kaplan-Meier survival curves stratified according to VEGF negative vs. VEGF positive tumors (A) [48] and prognostic factors associated with survival in multivariable analyses (B) [48]

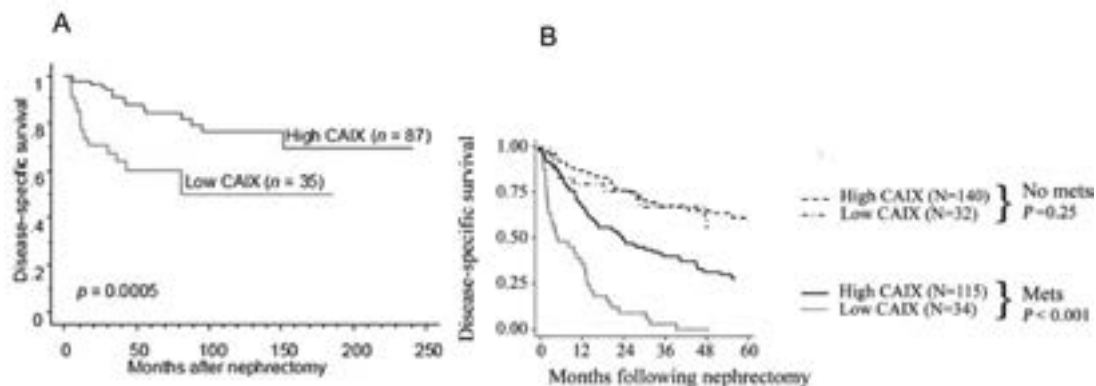


Figure 4. Kaplan-Meier survival curves stratified according to high levels of CAIX vs. low levels of CAIX in patients with clear cell renal cell carcinoma (A) [56] and survival curves stratified according to CAIX expression and metastatic status (B) [57]

e) Ribosomal protein S6

Ribosomal protein S6 (pS6), a downstream mTOR target, has S6 kinase activity [65] and the phosphorylated S6 (pS6) protein affects its downstream targets, altering mRNA translation (Fig. 1). [66] pS6 is differentially overexpressed in metastatic clear cell RCC and appears to be associated with activation of the mTOR pathway. [67] pS6 is a predictor of survival in both localized (HR: 3.14, $p=0.002$) and metastatic RCC (HR: 1.55, $p=0.04$). [67] Indeed high expression of S6 kinase ($p=0.02$) predicted response to temsirolimus in 20 patients [68] and may prove to be useful in predicting optimal biologic doses of mTOR inhibitors (i.e. everolimus) [69].

f) Protein Kinase B (pAkt)

pAkt, also called protein kinase B, regulates both growth and survival mechanisms by phosphorylating a wide spectrum of substrates in the cytoplasm and the nucleus (Fig. 1). [70] In univariable, but not multivariable, analyses, elevated pAkt immunostaining was associated with higher grade ($p=0.04$), higher rate of metastatic disease ($p=0.004$) and poorer RCC-specific survival ($p=0.01$). [71] Others reported a favorable prognosis in localized RCC with high pAkt expression (HR: 0.66, $p=0.3$, Fig. 5A). [67] Conversely, poor prognosis was reported with high cytoplasmic pAkt expression in metastatic RCC (HR: 1.31, $p=0.2$, Fig. 5B). [67] It is noteworthy that nuclear pAkt expression was higher in localized RCC tissue than in metastatic RCC tissue. [67] As such, the localization of pAkt may be relevant for determination of its effect on tumor behavior and resulting prognostic value.

Tumor samples from a subset of patients ($n=19$) within a randomized phase II trial of temsirolimus in metastatic RCC were studied. [68] High pAkt expression may predict response to temsirolimus treated patients with advanced RCC ($p=0.07$).

Objective tumor response was observed only in patients with high expression of pAkt. Confirmation of these findings is necessary before conclusions can be made.

g) PTEN

PTEN is a tumor suppressor protein that is encoded by the tumor suppressor gene *PTEN* (Fig. 1). Upstream to mTOR, the phosphatase PTEN regulates the mTOR pathway by inhibiting Akt phosphorylation through PI3K. [72, 73] While PTEN mutation may be a rare event, *PTEN* loss occurs during carcinogenesis and is associated with adverse prognosis in RCC. [72, 73] PTEN expression is higher in tumors with lower T stage, non-clear cell RCC, and localized stage. High PTEN expression improves survival (HR: 0.74, $p=0.3$). [67] mTOR inhibitors may be most beneficial in patients with low PTEN expression. However, recently no correlation between baseline PTEN and temsirolimus efficacy was found in poor-risk metastatic RCC patients (Fig. 6). [74]

h) Alternative biomarkers

Survivin

Deregulation of apoptosis is a hallmark in human carcinogenesis, facilitating the acquisition of deleterious cancer traits, including loss of tumor suppressor genes, angiogenic changes and immortalization (Fig. 1). Survivin is a member of the inhibitor of apoptosis (IAP) gene family that has been found to control mitotic progression and induces changes in gene expression that are associated with tumor cell invasiveness. Survivin mRNA is selectively expressed during embryonic and fetal development, becomes undetectable or expressed at low levels in most differentiated normal adult tissues, and is overexpressed in human cancers, [75-79] including RCC [80]. Survivin is expressed in all RCC variants. [81] High survivin expression (Fig. 7) is associated with poor differentiation, more aggressive behavior

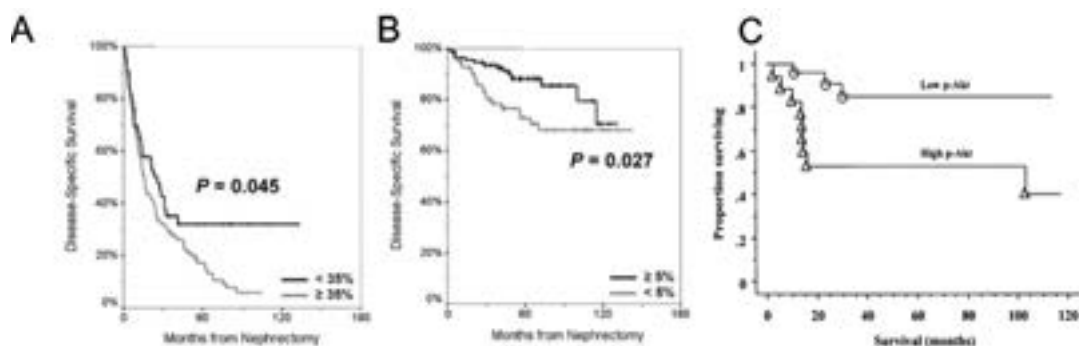


Figure 5. Kaplan-Meier survival curves stratified according to protein expression of cytoplasmic pAkt in metastatic renal cell carcinoma (A) [67] and stratified according to protein expression of nuclear pAkt in localized renal cell carcinoma (B) [67]

Temsirolimus	n	objective response	p-value
PTEN negative	72	6 (8)	1.0
PTEN positive	30	6 (20)	0.3

Figure 6. Correlation between baseline PTEN and temsirolimus efficacy in patients with poor-risk metastatic renal cell carcinoma [74]

(all $p < 0.05$) [81], and lower survival in clear cell RCC (even after adjusting for the effects of ECOG-PS, TNM and grade (HR: 2.4, $p < 0.001$) [82]. In localized RCC, high survival in expression predicted disease progression (HR: 1.9, $p = 0.02$). [82]

B7-H1

B7-H1 is a cell-surface glycoprotein within the B7 family of T-cell costimulatory molecules. [83] B7-H1 expression inhibits tumor-specific T-cell-mediated immunity through induction of T-cell apoptosis, impairs cytokine production, and diminishes the cytotoxicity of activated T cells. [84-88] High B7-H1 expression was associated with higher RCC-specific (HR: 3.92, $p < 0.001$) and all-cause mortality (HR: 2.37, $p < 0.001$) in 306 patients treated with nephrectomy for clear cell RCC. [89-91] In localized disease, tumors with high B7-H1 expression were more likely to metastasize (HR: 4.13, $p < 0.001$) even after adjusting for the effects of T stage, grade, and performance status (HR: 1.78, $p = 0.04$). [89] In localized clear cell RCC (HR: 3.32, $p = 0.002$), as well as in all RCC stages (HR: 3.25, $p < 0.001$), high B7-H1 expression in combination with survival expression

predicted higher mortality after adjusting for the effects of TNM stage, tumor grade, and ECOG-PS (n=298, Fig. 8). [92]

p53

p53 protein is a DNA binding molecule involved in the regulation of transcription (Fig. 1). [93] p53 has an important role in regulating cell growth and proliferation by stopping cell cycle and inducing apoptosis when DNA damage occurs. [94] p53 mutations allow detection through immunohistochemical staining due to its extended half-life. [95] p53 overexpression in papillary, chromophobe and clear cell RCC was recorded in 70, 27, and 12% of tumors, respectively. [96] p53 overexpression was an independent predictor of metastasis-free survival in patients with localized clear cell RCC ($p = 0.01$). [96] The prognostic role of p53 in RCC remains controversial with studies failing to show any independent prognostic value for survival (HR: 1.75, $p = 0.07$). [97] In other studies, its prognostic significance was limited to patients with localized disease only ($p = 0.002$). [98]

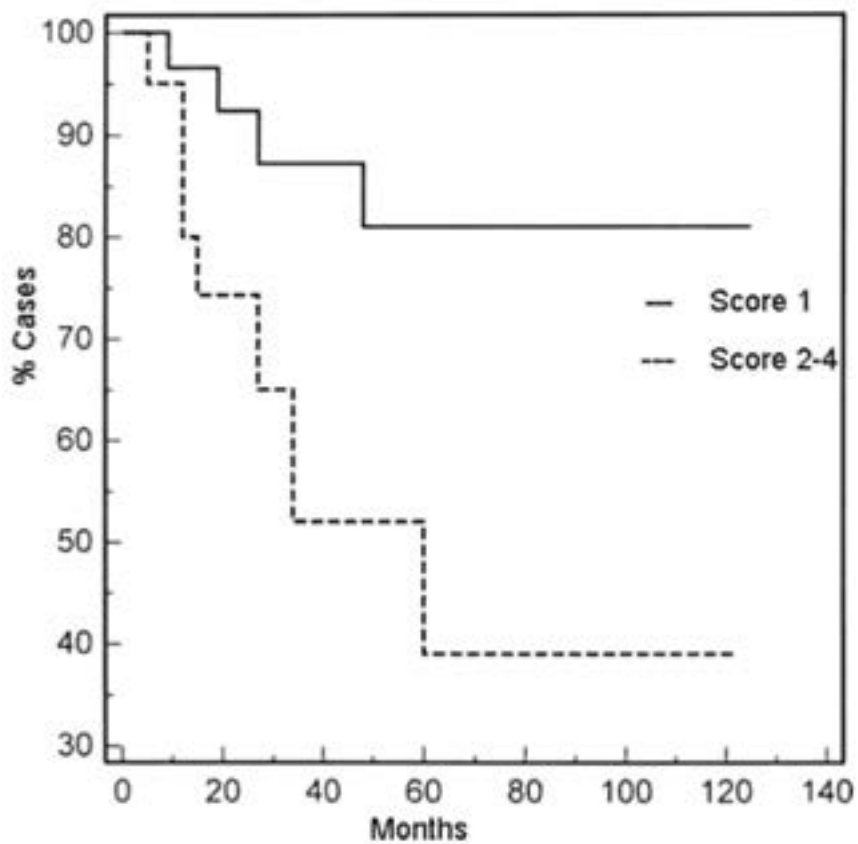


Figure 7. Kaplan-Meier survival curves stratified according to low expression (score 1) vs. high expression (score 2–4) of survivin of patients with clear cell renal cell carcinoma [81]

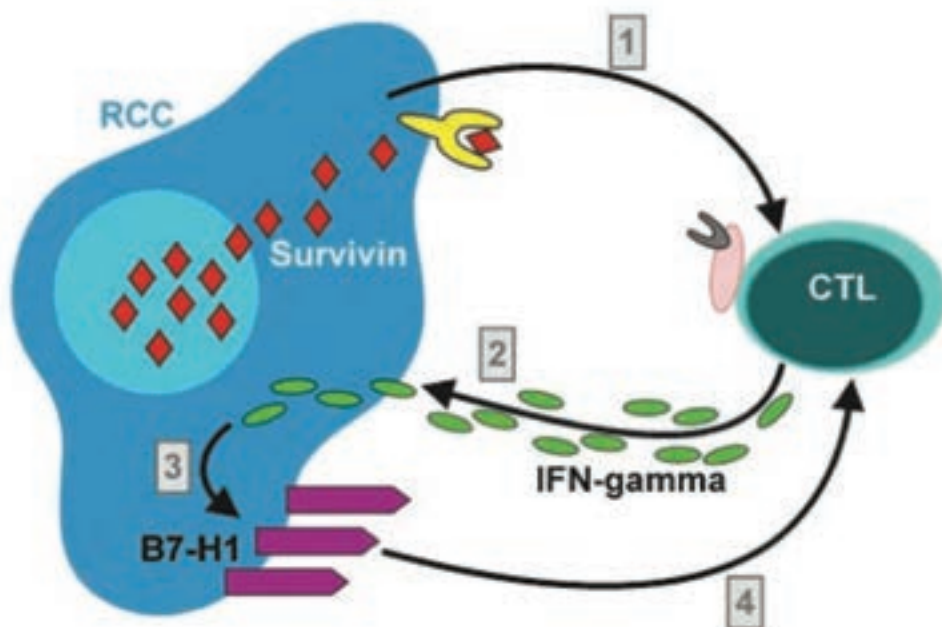


Figure 8. Illustration of proposed survivin and B7-H1 interaction [92]

Matrix metalloproteinases

The matrix metalloproteinase (MMP) family of enzymes is comprised of critically important extracellular matrix remodeling proteases whose activity has been implicated in a number of key normal and pathologic processes (Fig. 1). The latter include tumor growth, progression, and metastasis as well as the dysregulated angiogenesis that is associated with these events. As a result, these proteases have come to represent important therapeutic and diagnostic targets for the treatment and detection of human cancers. In RCC, MMP2 and MMP9 were found to be overexpressed in 67–76% and 43% of tumors, respectively. [99–101] In addition, overexpression of MMP2 and MMP9 was more common in non-clear cell RCC tumors. MMP2 and MMP9 overexpression were associated with aggressive behavior, tumor grade, and survival. [99–101] These associations are important, as there are several synthetic (i.e. batimastat, marimastat) and natural (i.e. broad statins) matrix metalloproteinase inhibitors that could help prevent and/or treat MMP overexpressing cancers. [102]

Insulin-like growth factor II mRNA-binding protein 3 (IMP3)

IMP3 is an oncofetal RNA-binding protein that regulates transcription of insulin-like growth factor II mRNA. IMP3 is expressed in developing epithelium, muscle, and placenta during early stages of human and mouse embryogenesis, but it is expressed at low or undetectable levels in adult tissues. IMP3 expression has been associated with cell proliferation and invasion in various cancers. In RCC, IMP3 is associated with higher RCC stage, grade, sarcomatoid differentiation and cancer-specific mortality. In a cohort of 371 patients with localized clear cell, papillary, chromophobe, and unclassified RCC, Jiang et al. reported that tumor cell IMP3 expression was significantly associated with progression to distant metastases and death, even after multivariable adjustment for the effects of patient age, sex, tumor size, stage, grade, and histological subtype (Fig. 9). [103] The prognostic value of IMP3 was externally validated in 716 clear cell RCC tumors showing that IMP3 expression was significantly associated with advanced T stage and grade, increased regional lymph node involvement, and distant metastases, as well as an increased likelihood for coexistent coagulative tumor necrosis and sarcomatoid differentiation. [104] In addition, even after multivariable adjustment for prognostic features comprising the SSIGN score, positive IMP3 expression was independently associated with an increased risk of death from RCC. In a recent article, Jiang et al. have shown that addition of IMP3 expression to tumor stage improves its prediction of metastasis. [105] IMP3 expression is a predictor of metastatic progression and death from RCC and

assessment of IMP3 expression may prove useful to identify at risk patients who might benefit from aggressive adjuvant therapy after primary tumor resection. Ultimately, IMP3 and the IGF pathway may provide useful targets to improve clear cell RCC therapy; however, further studies will be warranted before any definitive conclusions can be made.

Ki-67

Ki-67 is a cell proliferation marker [106] that is associated with an aggressive phenotype in clear cell RCC. [107–110] High Ki-67 expression predicts higher recurrence rates (HR: 1.05, $p=0.02$) [111] and worse survival (HR: 1.95, $p<0.001$) [26, 112–114]. Interestingly, the combination of Ki-67 and CAIX (HR: 1.76, $p<0.001$) surpassed the prognostic ability of nuclear grade in cancer-specific mortality analyses. [110]

Caveolin-1

Caveolin-1 is a structural component of caveolae. These are plasma membrane microdomains involved in the intracellular signaling pathways that regulate cell adhesion, growth and survival. [115] Increased caveolin-1 expression has been associated with a poor clinical outcome in several cancers such as prostate, lung, and esophageal malignancies. [116–123] Membranous caveolin-1 is expressed in 86.4% of clear cell RCCs and less than 5% of each chromophobe or papillary RCCs. Caveolin-1 coexpression with Akt/mTOR pathway components portended worse survival (HR: 2.13, $p<0.001$). [124] Others could, however, not confirm these findings (HR: 1.35, $p=0.9$). [125]

Tumor necrosis

Controversy exists regarding the importance of tumor necrosis in RCC prognostics. Tumor necrosis represents one of the components of the Leibovich scoring algorithm. [126] Previous evaluation of tumor necrosis as a potential marker for RCC mortality and recurrence revealed that it confers no added value when standard clinical and/or pathologic tumor characteristics were considered (Fig. 10A). [107, 127–129] Tumor necrosis improved prediction of survival in patients with localized RCC ($p=0.03$) but not in patients with metastatic RCC ($p=0.4$). [107] To improve its prognostic ability, Klatte et al. suggested quantifying the extent of tumor necrosis, instead of dichotomizing between its presence vs. its absence (Fig. 10B–C). [129] Added value and external accuracy remain to be proven.

C-reactive protein

Several investigators examined the prognostic significance of C-reactive protein. For example, C-reactive protein was a strong predictor of metastasis ($p<0.001$) and overall mortality ($p<0.001$) after

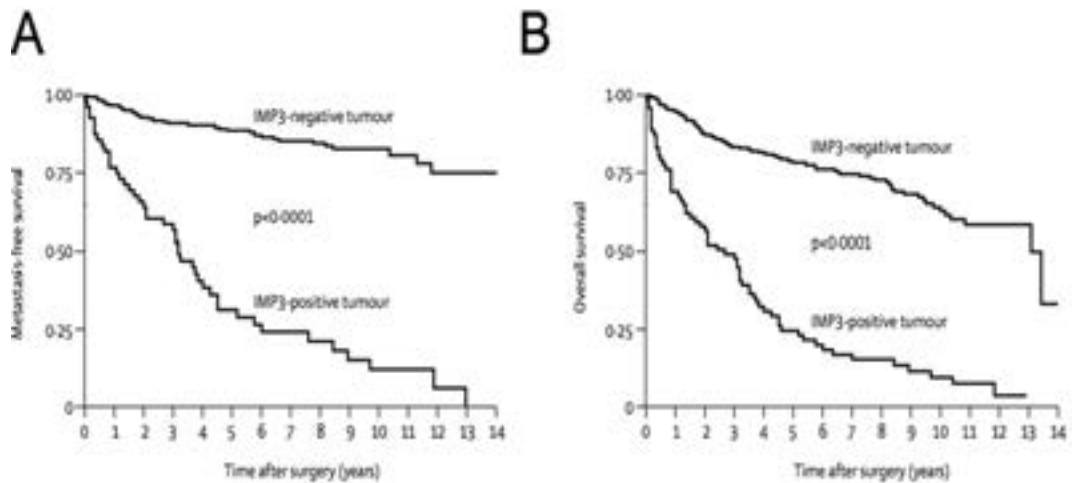


Figure 9. Kaplan-Meier metastasis-free survival (A) and overall survival (B) curves stratified according to IMP3 status [103]

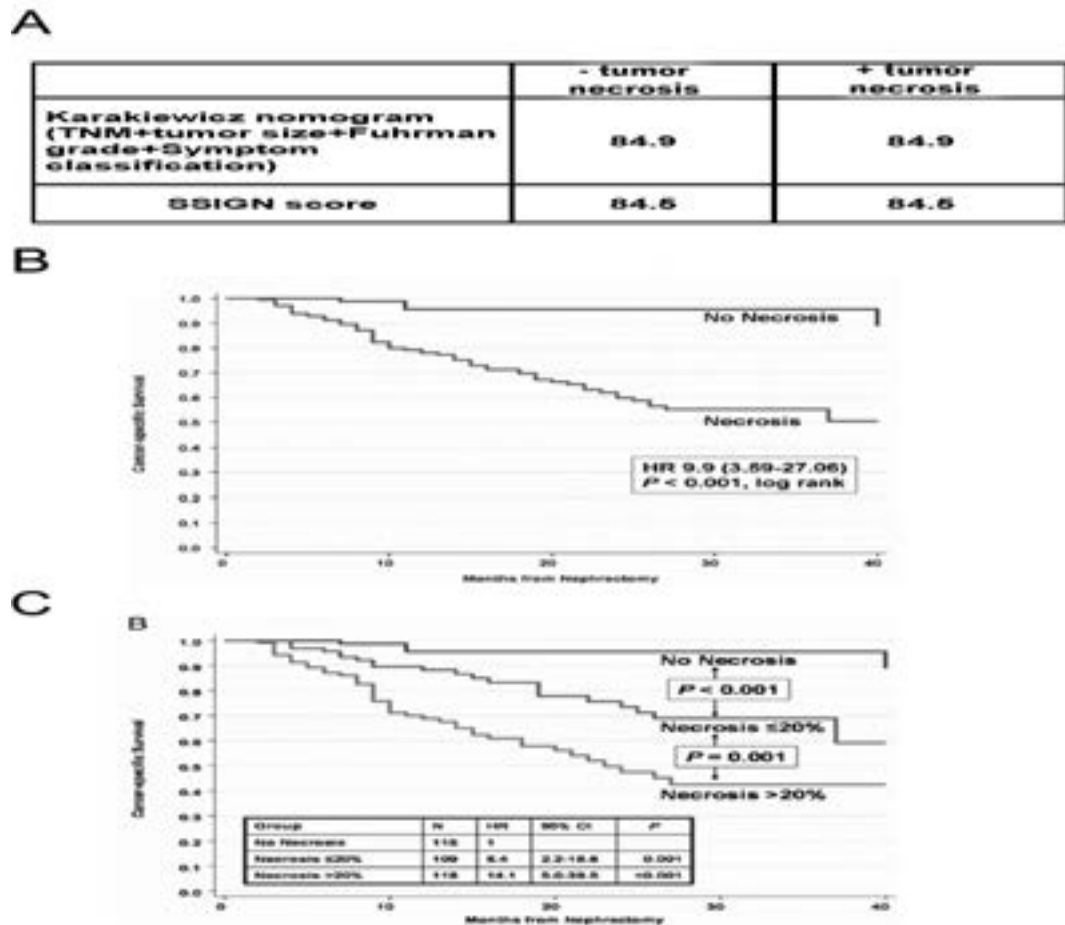


Figure 10. Predictive accuracy estimates of the Karakiewicz nomogram and the SSIGN score with and without integration of tumor necrosis (A) [127] Kaplan-Meier survival curves stratified according to presence and absence of tumor necrosis (B) [129] and according to the extent of tumor necrosis (≤20 vs. >20%) (C) [129]

nephrectomy for localized RCC in 130 patients. [130] C-reactive protein increased the predictive accuracy of several established clinical and pathologic predictors by 3.7% ($p<0.001$). [131] A gain of 10% (76.6% vs. 86.5%) was reported by Iimura et al. in a different cohort ($n=539$) within an external validation (Fig. 11). [132] In consequence, this inexpensive and widely available biomarker is highly promising. Its capability to predict response to targeted therapy as a predictive marker remains to be proven.

Vimentin

Vimentin a cytoplasmic intermediate filament, is not usually expressed in epithelial cells (Fig. 1). Vimentin expression is common in clear cell (26-51%) and papillary RCC (61%). [133-137] Others found low frequency of vimentin staining in clear cell RCC. [138] Vimentin overexpression (30 to 53%) predicted poor prognosis ($p<0.007$), independent of the effect of T stage and grade. [137]

Fascin

Fascin is a globular actin cross-linking protein involved in cell adhesion and motility (Fig. 1). High fascin expression ($p<0.001$) correlated with sarcomatoid transformation, high tumor stage ($p=0.008$), high tumor grade ($p=0.002$), and larger tumor size ($p<0.001$). [139] Moreover, fascin expression predicted metastatic progression (HR: 7.2, $p<0.001$). Other investigators confirmed these findings. [140]

2. BLOOD-BASED BIOMARKERS

a) Thrombocytosis

The prognostic potential of thrombocytosis was reported in five studies. [141-145] However, the question of whether a biomarker can improve the ability of established predictors of cancer outcome requires more than the conventional univariable and multivariable analyses, with associated hazard rates and p -values. In order for a biomarker to be clinically useful, it must add unique predictive information, thus improving the performance of a predictive model constructed without the new biomarker by a

significant margin. Thrombocytosis did not add any meaningful value (+0.3%) to a model that comprised TNM stage, age, tumor size, Fuhrman grade, histological subtype, and preoperative hemoglobin ($n=1828$). [141] In consequence, the prognostic value of thrombocytosis remains to be proven.

b) Neutrophils

Several investigators demonstrated independent predictor status for peripheral blood and intratumoral neutrophils, when mortality was considered as an endpoint. [146-150] In a phase II study, Donskov et al. evaluated 63 metastatic RCC patients treated with interleukin-2 or interleukin-2+histamine. [148] High peripheral blood neutrophil counts predicted very poor survival and lack of response to interleukin-2 alone or interleukin-2+histamine. Serum neutrophils were also included among six most informative predictors in the Heng et al. [10] survival model. In addition, the presence of intratumoral neutrophils also independently predicted shorter recurrence-free survival (hazard ratio [HR]: 3.0, $p<0.001$), higher RCC mortality (HR: 3.5, $p<0.001$), and poor overall survival (HR: 3.1, $p<0.001$) in 121 patients with localized RCC. [151] Finally, intratumoral neutrophil counts improved the predictive accuracy of the Leibovich scoring algorithm [152] from 74 to 80%. Despite those promising results, the confirmation of added value when intratumoral neutrophils was considered was not confirmed. This variable awaits its external validation.

c) VEGF

Plasma VEGF levels correlate strongly with tissue VEGF expression ($p=0.01$). [50] Similarly, serum levels of VEGF correlate with clinical stage and tumor grade of RCC. [50, 153, 154] Vascular invasion ($p=0.03$), tumor size ($p=0.01$), [154] and survival. [153-155] For example, in 302 metastatic RCC patients, baseline serum VEGF levels predicted progression-free survival (HR: 1.19, $p<0.001$) and overall survival (HR: 1.39, $p<0.001$) after treatment. [155] However, serum VEGF failed to achieve independent predictor status in other studies. [153-157] This may be due to analytical problems in some of the studies. It has

	MVA model without CRP	MVA model with CRP	P-value
Karakiewicz et al n=313	81.6	85.3 (+3.7)	<0.001
Iimura et al (dev: 249 - val: 290)	76.6	86.5 (+9.9)	<0.001

Figure 11. Predictive accuracy estimates of two models with and without integration of CRP [131, 132]

been previously found that VEGF levels are higher when measured in serum than when measured in plasma.[158] Since VEGF is present in platelet granules and is released upon platelet activation, the higher levels of VEGF in serum were likely due, at least in part, to those released from damaged platelets, making the quantification of non-platelet derived VEGF less accurate. After sunitinib exposure, lower VEGF plasma levels predicted response to therapy ($p < 0.05$) [159] and decreased risk of disease progression (HR: 1.96, 95% confidence interval: 1.47 – 2.45) [160]. Low baseline soluble VEGF levels also predicted response to sunitinib after bevacizumab failure. [161] Conversely, VEGF levels failed to predict response to sorafenib according to RECIST criteria ($p = 0.6$), but was associated with overall survival in these patients ($p = 0.01$). [162] The validation of VEGF levels as a prognostic factor in targeted therapies is currently being evaluated in two separate trials (NCT00538772, NCT00930345).

d) Serum amyloid A

Human serum Amyloid A (SAA) is an HDL-associated lipoprotein known to play a major role as a modulator of inflammation and in the metabolism and transport of cholesterol. SAA is a potentially useful biomarker to monitor patients harboring human tumors such as gastric, nasopharyngeal, and lung cancer. In RCC, SAA concentrations were higher in metastatic patients and SAA levels were an independent predictor of all-cause survival.[163] A protein pattern, including SAA identified by surface enhanced laser desorption/ionization time-of-flight mass spectrometry (SELDI-TOF-MS) analysis of serum samples of 50 clear cell RCC patients and 50 volunteers was able to discriminate the two groups with a sensitivity of 70–78% and a specificity of 82–92%, respectively.[164] One major problem with the use of SAA, an acute phase reactant, as a potential serum marker in human cancer patients, is the fact that its elevation in the serum of patients is suggested to be of liver origin rather than a tumor-cell product. Indeed, SAA level in the blood may elevate up to 1000-fold in response of the body to various injuries including trauma and various inflammations in addition to neoplasia.

e) CAIX

Recently, an assay for detecting low levels of CAIX in blood was developed. [165] Higher serum CAIX levels is correlated with clear cell RCC variant (86%, $p = 0.001$), but not with tumor stage or grade. [166] Others found a correlation of higher serum CAIX levels with tumor size and disease stage ($p = 0.004$), [167, 168] as well as disease recurrence ($p = 0.001$) [168] and mortality ($p = 0.048$) [169]. An ongoing trial will determine the prognostic value of serum CAIX as a solid biological marker of treatment response to immunotherapy and/or targeted therapy in patients with metastatic RCC (NCT00942058).

f) Neutrophil gelatinase-associated lipocalin (NGAL)

NGAL is a protein upregulated in 'distressed' cells, such as the case when in the presence of a tumor. [170] It demonstrated high correlation with matrix metalloproteinase-9, a protein involved in the degradation of the extracellular matrix which relates to tumor invasion and metastases. [171] NGAL has a protective effect against acute ischemic injury [172], and is high in several human cancers. [173] Above-threshold level of NGAL resulted in decreased progression-free survival relative to those with below-threshold level of NGAL in patients treated with sunitinib (3.4 vs. 8.2 months, $p = 0.03$). [174]

g) Insulin-like growth factor-1

While there are many varied roles of insulin-like growth factor I (IGF-I), and it exists in different bio-compartments, there is abundant scientific evidence demonstrating that IGF-I is an important metabolic biomarker associated with a variety of health- and exercise-related outcomes. In most cases (muscle, bone, tendon, body composition, and cognitive function), elevated IGF-I concentrations are considered beneficial; however, cancer remains a notable exception. In a series of 256 RCC patients, serum IGF-1 levels were associated with all-cause survival after adjusting for the effects of tumor stage. [175] While interesting, the prognostic role of IGF axis in RCC is only in its infancy.

3. URINE MARKERS

The urinary nuclear matrix protein 22 (NMP-22) is a Federal Drug Administration (FDA) approved biomarker for bladder cancer screening and monitoring. [176-178] It has also been examined as a diagnostic marker for RCC. Three studies have shown that urinary NMP-22 levels were higher in RCC patients compared to those in control subjects (all $p \leq 0.005$).[179-181] Well-done, large-scale studies are needed to establish the utility of NMP-22 in RCC diagnosis and potentially prognosis.

IV. USE OF BIOMARKERS IN PROGNOSTIC MODELS

A prognostic model for prediction of survival in RCC using primarily molecular markers as predictors (p53, CAIX, gelsolin, imatinib, and metastatic status) was 79% accurate ($n = 318$; **Table 2, Fig. 12**). [97] Subsequently, the same group of authors evaluated a slightly different model of molecular markers (CAIX, PTEN, imatinib, p53) and was 64% accurate ($n = 150$). Adding ECOG-PS and tumor stage increased predictive accuracy by 4%. Predictive accuracy relying on clinical and molecular markers

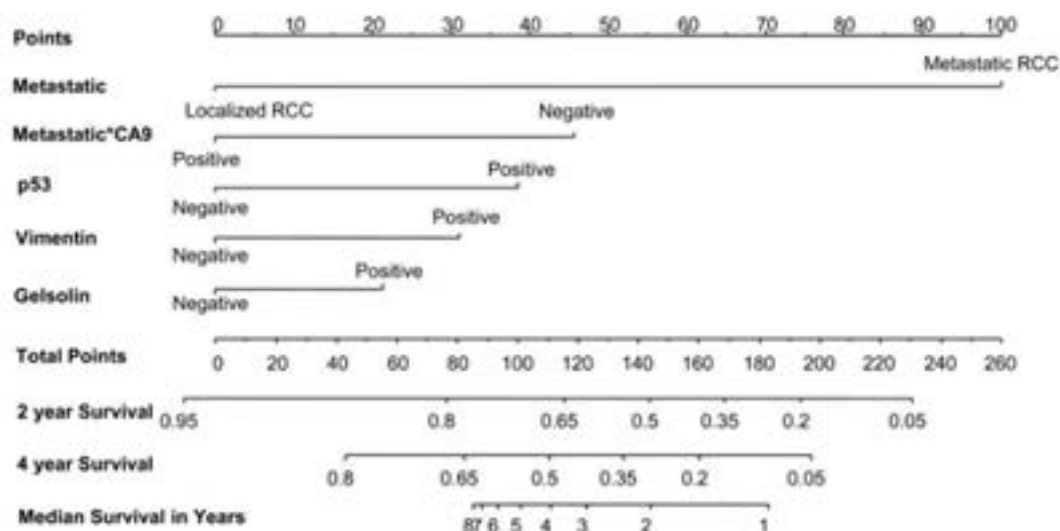


Figure 12. Prognostic model for prediction of 2- and 40-year overall survival relying on metastatic status, metastatic CAIX, p53, vimentin and gelsolin in the format of a nomogram [97]

(68%) was statistically significantly higher ($p=0.003$) than that of the UISS system alone (62%). [182] The integration of the BioScore[26] (tumor expression levels of B7-H1, survivin, k-67) in clear cell RCC patients ($n=634$) to the UISS and the SSIGN models gained respectively 4.5 and 1.6% accuracy (Table 4).

Others evaluated the prognostic value of biomarkers with clinical and/or pathological characteristics in patients with advanced RCC treated with VEGF- or mTOR-targeted therapies or immunotherapy. [8, 146, 183-185] Recently, factors associated with longer overall survival within sunitinib-treated patients included time from diagnosis to treatment of more than a year, ECOG-PS, corrected calcium, absence of bone metastases, low LDH, and high hemoglobin. [186] Factors associated with longer overall survival within interferon-alpha treated patients included: male gender, absence of bone or lymph node metastases, lower LDH, higher hemoglobin, corrected calcium, higher neutrophil count, and interval from diagnosis to treatment of more than a year. [186]

In anti-VEGF therapy naïve metastatic RCC, hemoglobin ($p<0.001$), corrected calcium ($p<0.001$), KPS ($p<0.001$), time from diagnosis to treatment ($p=0.01$), neutrophils ($p<0.001$) and platelets ($p=0.01$) were adverse prognostic factors for overall survival (accuracy: 73%, $n=645$). [10]

V. CONCLUSIONS

The search for predictive and prognostic markers stems from the unpredictable nature of RCC in its localized, locally advanced and metastatic stages. A

number of such markers emerged. Of those, many show promise by virtue of stratifying the survival curves or discriminating between stage distributions (eg. CAIX, VEGF). Other markers achieved independent predictor status (e.g. k-67, serum CAIX) when their contribution to the prediction of the endpoint of interest was examined. Finally, the most valuable ones (C-reactive protein, BioScore (survival, B7-H1, k-67)) demonstrated an added value when combined accuracy was quantified without and with their contribution. Independent confirmation of their value, within external validation studies and using standardized measurements, represents an unconditional requirement prior to their integration into routine clinical practice. Validation of informative markers of response to targeted agents represents a priority consideration.

The value of novel markers is required within the framework of existing markers and models. For example, a recent model that relies on clinical and radiological information can predict the probability of mortality from one to ten years after nephrectomy.[21] It relies on clinical and radiological variables and results in 84-88% accuracy. A similar model that integrated pathological characteristics resulted in 88-89% accuracy for predictions of mortality from one to ten years after nephrectomy.[20] Neither of the models relied on biomarker data. The highly accurate nature of these models raises the bar for novel biomarkers, as it is relatively difficult to improve accuracy beyond the 90% mark. Consequently, the dearth of models capable of accurately predicting the probability of response to targeted therapies represents an important unmet need in the field of RCC prognostics.

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Treatment of Localized Renal Cell Carcinoma

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Treatment of Localized Renal Cell Carcinoma

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I. INTRODUCTION

Due to the increased use of diagnostic imaging more kidney tumours are being detected incidentally, leading to an increased incidence of asymptomatic organ-confined small renal masses (SRMs) [1]. SRMs account for 48% to 66% of renal cell carcinoma (RCC) diagnoses [2]. This has resulted in an increased incidence of RCC over the last three decades. There is controversy on the mortality rates of RCC. Some authors mention that mortality rates are rising. Cancer statistics are showing the opposite (38% in 1997 vs. 25% in 2007) [3,4]. Current treatment should be reassessed [1]. Today, the standard of care for clinically localized RCC is surgery predominantly in the form of nephron-sparing surgery (NSS) because of the durable oncologic outcome and overall survival. Active surveillance (AS) and minimally invasive ablative technologies have emerged as potential alternatives to surgery in selected patients. In this chapter, we critically review the recent data on the management of localized RCC with the objective of arriving at a general consensus.

II. METHODS

A comprehensive review of the Medline literature from January 1, 2004 to April 11, 2010 regarding the treatment of localized RCC was conducted. The combination of the following words was used: renal cell carcinoma, nephrectomy (MeSH major topic), surgical procedures, minimally invasive (MeSH major topic), nephron-sparing surgery, cryoablation, radiofrequency ablation, surveillance and watchful waiting. Search was limited to English papers. Further references were identified from the reference list of retrieved articles. As few randomised studies were available the majority of the conclusions

were drawn from case series or comparative cohort studies, both prospective and retrospective. A preliminary draft was composed by the chairman of the group and circulated throughout the members for modifications. After considering all modifications a definite draft was composed, reviewed and supported by all members of the group. In case of statement disagreement consensus was reached by majority.

III. ACTIVE SURVEILLANCE FOR LOCALIZED RCC

1. INTRODUCTION

SRMs are not uncommonly detected in elderly patients or those with significant co-morbidities. These patients have a higher risk of perioperative mortality and morbidity after treatment and a limited life expectancy that often appears to exceed the risk of cancer progression. Moreover, a significant proportion (up to 20%) of these SRMs is benign when biopsied or removed [5-9]. Even when those SRMs are confirmed to be RCC, most have slow growth rates and infrequently metastasize during the first few years after diagnosis [10]. These issues are important arguments to support an initial surveillance period for selected patients and reserve treatment for progression. Active surveillance (AS) of SRMs is now increasingly performed in carefully selected patients with an emerging experience to support this treatment option [2,7,11-29].

2. SMALL RENAL MASSES AND THEIR NATURAL HISTORY

Most AS studies of SRMs have relatively few subjects and are retrospective with limited follow-up and pathological confirmation of malignancy. Therefore Chawla et al performed a meta-analysis of several

small AS series and their own institutional cohort [2,12-14,16-18,20,21]. A total of 234 untreated SRMs had a mean follow-up of 34 months. The majority of the lesions (mean size of 2.60 cm, range 1.73 to 4.08 cm) demonstrated a slow growth rate (mean rate 0.28 per year, range 0.09 cm to 0.86 cm per year). Metastasis was reported in 1% of the cases during AS. In total, 86% of the lesions were smaller than 4 cm in maximal diameter at presentation. Initial tumour size did not predict overall growth rate ($P=0.46$). An absolute cut-off for selecting patients for a surveillance strategy does not exist since at present, the metastatic potential of observed tumours cannot be predicted. (Fig. 1) There are several important considerations in interpreting the results of the Chawla meta-analysis. Many tumours were not biopsied and may have been benign. Only 46% of the patients had pathological evaluation and the pathological analysis was incomplete in many cases. Tumours with rapid growth often underwent surgery because of concern for progression to metastasis. A rapid growing mass is arbitrarily defined as one that doubles its volume within 1 year [2]. Some degree of selection bias may have been present by inadvertently selecting patients with slower growth rates during an initial period of AS. Finally, the series had short durations of follow-up (mean 30 months) which may not reflect the intermediate and long-term growth potential of these tumours. Overall, the favourable results in patients undergoing AS should be interpreted as preliminary as these issues could bias the findings [21].

Similar findings supporting the absence of baseline predictive factors are found in two recent series from Cleveland and New York. There were no reported

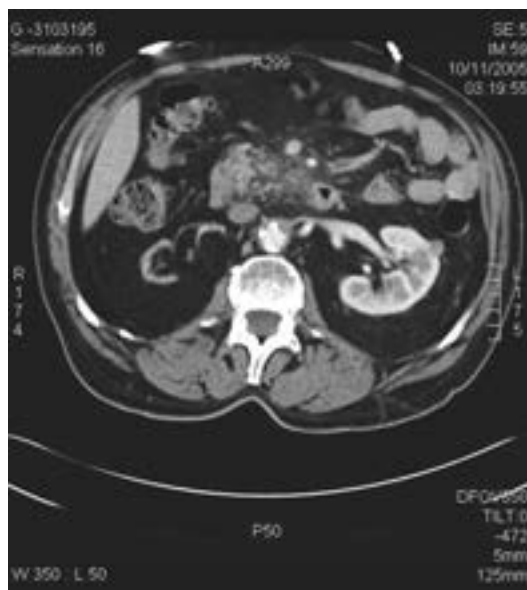


Fig. 1: CT showing atrophic right kidney and left sided small renal mass of uncertain pathology

differences in patient's or tumour characteristics between those tumours that locally progress and those that remain stable [28,29]. Crispen et al reported the radiographic growth kinetics of renal tumours during a period of AS. Smaller tumours seemed to exhibit significantly faster volumetric growth than larger tumours. The authors found that 39% (68 of 173) of patients on AS crossed over to treatment within 2 years of follow-up for a variety of reasons including patient and physician preference. AS is associated with a low rate of progression to metastatic disease (1.3%) (2 of 154). However, the actual progression rate may be higher than reported because of several factors including the relatively short duration of follow-up, inclusion of benign disease in some series, selective intervention for tumours demonstrating accelerated growth kinetics, and the selection bias inherent to retrospective data sets [29].

3. PROGNOSTIC FACTORS FOR PROGRESSION

a) Tumour size

The favourable results of the Chawla et al analysis are consistent with data about biological aggressiveness of SRMs. Up to 20% of renal masses are actually benign [5-9]. Only about 20 to 25% demonstrate potentially aggressive characteristics [5,7,30].

Smaller renal tumours are more likely to be benign or to be of lower grade than larger tumours [31] with several studies showing increased growth potential of SRMs with a diameter > 3 cm [5,7,32]. Kunkle et al reported that the risk of biopsy proven metastasis goes up 22% with each one centimeter increase in tumour size [24]. However, Remzi et al could not find a clear correlation between tumour size and benign histology in an analysis of histopathological parameters in 287 tumours ≤ 4 cm in diameter [7]. They found that Fuhrman grades G3 and G4, higher pathological stage (pT3a or greater) and metastatic disease were seen significantly more frequently in tumours > 3 cm in diameter. This difference was however not observed when masses ≤ 2 cm in diameter were compared with those measuring 2.1 – 3.0 cm. Taking into account that measuring tumour diameters is difficult, is subject to observer reliability, and is frequently based on different imaging modalities, some believe that AS strategies should be limited to patients with tumours ≤ 3 cm [7]. In general however, ≤ 4 cm is used to conform to stage T1a for RCC. Not all SRMs can be deemed harmless and even very small tumours may progress to metastatic disease. Three recent large single-center studies indicate that amongst renal cancers 3-4 cm in size, 14-26% are high grade (grade 3 or 4) and 12-36% locally invade peri-renal fat (stage pT3a) [7,8,32]. These 3 series report that small 3-4 cm cancers have a higher metastatic

risk approaching 6-8% [7,8,32]. The changes in morphological characteristics of the tumour above 3 cm reported by Remzi et al were more extreme than in other series. Klatte et al reported their experience with 1,208 patients who underwent nephrectomy for small solid renal tumours. They found that the incidence of metastatic disease in tumour ranges of 0.1 to 1.0, 1.1 to 2.0, 2.1 to 3.0 and 3.1 to 4.0 cm was 7%, 6%, 5% and 8%, respectively ($P = 0.322$) [8]. Nguyen and Gill analyzed the national 1998-2003 Surveillance, Epidemiology, and End Results (SEER) data-set and documented a 5.2% prevalence of metastasis at presentation in 8,792 patients with a small (< 4 cm) pathologically-confirmed renal cancer [33]. For size sub-categories ≤ 1 , 1.1-2, 2.1-3, and 3.1-4 cm, prevalence of metastasis at diagnosis was 1.4%, 2.5%, 4.7% and 7.4%, with 5-year cancer-specific mortality of 4.2%, 4.3%, 5.5% and 7.9%, respectively. For small renal cancers < 4 cm, 5-year cancer-specific mortality for all patients, and those without and with metastases at presentation was 6.2%, 2.9% and 74.3% respectively. For each cm increase in primary cancer size, the calculated prevalence of metastases increased by 3.5% [33]. In all these reports, patients presenting with metastases and those with symptomatic primary tumours were undoubtedly included so the conclusions should be applied to the usual asymptomatic properly staged SRM patient on AS with caution as the AS series report metastases in up to 2.3% [34]. However, when considering AS, tumour size alone may not be a reliable indication or trigger for treatment of SRMs [5,7-9].

b) Growth rate

Chawla et al could not identify a significant correlation between initial tumour size and growth rate in their analysis of 157 post incidentally detected tumours from 5 observational series ($P = 0.46$) [2,12-14,18,21]. This has been confirmed by Crispen et al [29]. Therefore, at this time, initial tumour size may not predict subsequent growth rate. Most authors report the mean tumour growth rate to be between 0.06 cm/yr and 0.21 cm/yr for tumours < 4.0 cm in size [2,17,25,26,35]. Growth appeared to be slow even in those patients diagnosed with larger masses [19]. For example, the mean lesion size in the series of Lamb et al was 7.2 cm (range 3.5 – 20.0) with a mean growth rate of 0.39 cm per year [19]. A recent study from the Memorial Sloan-Kettering Cancer Centre has shown that small renal tumours (≤ 3.5 cm) were similar to larger tumours in subtype and growth rate. Faster-growing tumours were more likely to be RCCs of higher grade. No significant correlation was found between the reciprocal of doubling time and initial tumour volume, histological subtype, or Fuhrman grade [36]. One must realize that a subset of patients may have small rapidly growing renal tumours with aggressive behaviour while under AS.

Volpe et al reported that eight renal masses (25%) doubled their volume within 12 months, and one patient progressed to metastatic disease [2]. In the study by Siu et al, a 3-cm mass that had not changed in size for 6 years doubled in size over 6 months, and metastatic disease developed [37]. The value of volume doubling time is still uncertain. Nevertheless, Lee et al suggested that more accurate assessment of tumour growth rate and volume doubling time may be useful for understanding the natural history of renal tumours [38].

c) Histology

A SRM has been reported to be more malignant if growth is observed. However in the Canadian prospective, multicenter study with needle biopsy, there was no difference in growth rate between benign and malignant tumours [39]. However, it remains difficult to predict biological behaviour of SRMs, even if they do not show growth. Lack of growth on serial CT scanning is not a reliable predictor of benign histology as even RCCs with zero growth rates have demonstrated progression. Kunkle et al revealed that 26% to 33% of renal tumours followed by AS do not grow at 29 months median follow-up. Importantly, these tumours with zero growth rates had similar rates of malignancy compared to growing lesions (83% and 89%; respectively; $P = 0.56$) [22]. The authors concluded that growth rate does not correlate with prognosis [22]. These observations and those of the Canadian study raise questions about the biology of SRMs that need to be better understood to define better prognostic factors.

d) Age

A meta-analysis of published observational series [2,11,16-18,21] demonstrated an inverse correlation between increasing age and tumour growth rate. Kouba et al found a more rapid growth in younger patients (≤ 60 years) (0.77 cm versus 0.26 cm per year) [40]. Therefore surveillance is currently not recommended in fit and young patients [10].

e) Progression to metastatic disease

There is no published report of metastasis occurring in the absence of tumour growth but the Canadian series has reported 2 patients who were found to have metastases at 4 and 12 months after enrolment while their SRMs were about 2 cm in diameter and there had been minimal or no growth (average 0.5 mm/yr, $P = 0.41$) [39]. The low rate of metastatic progression in most AS series may be influenced by the short follow-up as well as, the benign histology of a number of solid renal masses, the small tumour size and the retrospective nature of the studies. Youssif et al reported a surveillance study with a mean of 47.6 months follow up. Two patients developed metastatic disease (5.7%; 2 of 35) after 29 and 40 months, respectively, in a group

of tumours < 4 cm in diameter. The renal masses in these 2 patients had a growth rate of 0.95 cm/year and 0.9 cm/year, which is a faster growth rate than the mean of 0.15 cm/year observed in the 17 patients who were still being followed actively at the time of last follow-up. Until we have more information on this important prognostic factor, faster growth during the surveillance period should alert physicians to the potential risk for progression to metastatic disease and be considered as a trigger point for a treatment recommendation [26].

f) Imaging

Imaging characteristics do not provide a reliable prognostic factor for progression at this time [9]. No parameter was able to predict progression or overall prognosis [21,30,32,37,41]. No difference was noted in tumour size at presentation or tumour growth rate between oncocytomas and RCCs in the meta-analysis by Chawla et al [21]. When comparing independent computerized tomography (CT) measurements of tumour size, differences less than 3.1 mm for inter-observer and less than 2.3 mm for intra-observer evaluations are situated within the range of measurement variability and should not be attributed to tumour growth. As tumour volume is exponentially related to tumour diameter, the accuracy of measuring tumour volume is associated with a greater error (inter-and intra-observer variability for tumour volume: 2.515 mm³ and 2.075 mm³, respectively) [42]. Ficarra et al recently proposed The Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) classification of renal tumours that takes into consideration five anatomical aspects of the tumour plus its maximal diameter. The study demonstrated that the PADUA score is able to predict the risk of surgical and medical perioperative complications in patients who underwent OPN [43]. This classification differs from the R.E.N.A.L nephrometry scoring system recently proposed by Kutikov et al to quantify the anatomical characteristics of renal masses (size, location and depth) on computerized tomography (CT)/magnetic resonance imaging (MRI) [44]. The main differences are the definition of the sinus lines and the evaluation of the anatomical relationship between the tumour and the urinary collecting system or renal sinus [43]. Furthermore, SRMs are not necessarily spheroidal which increases the error in measuring tumour volume. Therefore, neither tumour size nor tumour volume are reliable parameters for defining management of SRMs [45].

Two papers addressed the histological diagnosis of SRMs on CT. One study showed that the enhancement pattern of double-phase helical CT was different among the subtypes of RCC, but did not differentiate between RCC and other solid tumours. All clear cell RCCs (n=29) showed a peak attenuation in the corticomedullary phase (CMP)

of > 100 HU (type A). All chromophobe cell RCCs (n=2) showed a peak attenuation value in CMP of < 100 HU (type B) and all papillary RCCs (n=5) showed a gradual enhancement with the attenuation value in the CMP of < 100 HU (type C). However oncocytomas (n=2) and metanephric adenomas (n = 2) also showed patterns similar to these subtypes of RCC. Therefore the diagnosis of oncocytoma and metanephric adenoma is unreliable on the basis of enhancement [46]. A more recent study showed that when using a multi-detector CT (MDCT) and thin overlapping reconstructions (3 mm section thickness, 50% overlap), renal cysts as small as 5 mm can be diagnosed with more certainty than is possible with standard reconstructions (5 mm thickness and no overlap). Of 45 masses between 5 and 10 mm, 38 (84%) could be characterized as cysts with the experimental protocol, compared with only 13 (29%) with the standard protocol. The overall number of indeterminate renal masses was reduced using the experimental protocol (86 of 161 lesions; 53%), compared with the standard protocol (101 of 146 lesions; 69%). Despite technical progress in technique, at this time, the majority of detected renal masses are smaller than 5 mm and cannot be characterized [47].

4. RENAL TUMOUR BIOPSY

A retrospective study by Remzi et al reported that 81.9% of all renal masses were RCC and only 17% were correctly defined as benign on preoperative CT. In total 42% of renal masses underwent surgery for benign lesions not correctly identified as benign on preoperative CT. Surgery could potentially have been avoided in these patients [9]. Thus, a more refined preoperative diagnostic evaluation, in particular needle biopsy is needed for defining management of SRMs [9] and can help in selecting patients suitable for AS [45]. Due to advances in biopsy and imaging techniques the results of needle biopsies have improved significantly [48]. The overall complication rate in these studies was low (<5%) and major complications were rare (< 1%). The most frequent complication was hemorrhage, which is almost always self-limiting. Renal tumour biopsy has therefore become a safe and accurate technique (45,49,50) that provides useful material for diagnosis in > 90% of cases in centres with expertise [49].

Several issues have prevented widespread adoption of pretreatment biopsy. Biopsy accuracy remains a concern although the first order question of malignant vs. benign is approximately 80% accurate when tissue is obtained. There remains up to 20% of biopsies that are non-diagnostic due to tumour misses and this rate varies with experience and tumour size [51]. Three prospective studies have evaluated CT-guided SRM biopsy. In these studies, ranges of biopsy accuracy for detecting benign and malignant tissue, histologic subtype, and Fuhrman grade were

89-96%, 70-76%, and 78-92%, respectively [52-54]. In the study of Schmidbauer et al, 42% of the renal masses were larger than 4 cm. While the authors report excellent results of core biopsy, we do not know what is the accuracy of CT guided biopsy in SRMs [54]. In the study of Lechevallier et al, results are not stratified by size; the median size of the masses evaluated is 4 cm, but there are masses of 15 cm in this series [52]. Furthermore, accuracy is based on those biopsies that were diagnostic. In the study of Neuzillet et al 9% of biopsies were non diagnostic. In the studies of Schmidbauer and Lechevallier only 3% and 21% of the biopsies failed, respectively. The corresponding figure was 37% in the 30 SRMs of \leq 3 cm. In view of those results grade and histological subtype accuracy remains controversial in SRMs [52-54]. As well, pathological confirmation in the study of Neuzillet was obtained only in 70.4% of the cases and in the study of Lechevallier in 50% of those patients with non metastatic lesions (surgery in 27 out of 52 patients) [52,53]. Most of the studies on biopsy exclusively in SRM are retrospective in nature and subject to the same limitations above exposed. The subject is reviewed in a recent paper of Laguna et al [55].

Several other issues include the difficulty with the diagnosis of oncocytoma versus hybrid chromophobe RCC. Waldert et al have recently shown that up to 17% of oncocytoma actually harbour hybrid chromophobe RCC [56]. The diagnosis of oncocytoma on biopsy cannot be relied on for being proof of a benign lesion and an uncritical surveillance approach. As about 45% of benign renal tumours are oncocytoma, this is a major problem for the diagnostic accuracy of renal biopsies [9].

The use of preoperative biopsy is likely to reduce unnecessary treatment if benign lesions are initially observed. Multiple tumours probably need to undergo multiple biopsies because if one of the tumours is RCC that does not mean that the other is RCC as well. Several new immunohistochemical and molecular factors are being evaluated as determinants of the aggressiveness of RCC and molecular profiling of SRMs is now possible [57,58]. Unfortunately, the available data on molecular markers are not yet valid enough for routine, clinical application [58]. Renal mass biopsy enhanced by molecular profiling will further help in decision making about AS. Further research will be required to define the utility and limitations of this approach [41].

5. SURVEILLANCE STRATEGY

An absolute cut-off for tumour size and growth rate that should prompt intervention during surveillance has not been well defined [25]. A working hypothesis has emerged that tumours beyond a diameter of 3 or 4 cm or those that double in volume in less than 12 months are at risk of progression and should

be treated [2,7,8,48]. A large multicentre series of incidental renal tumours revealed that a surveillance strategy should not be advised in patients with a renal tumour >4 cm, if biopsy confirms high Fuhrman grade regardless of the size, or if CT findings suggest advanced T stage [59]. AS with regular radiographic follow-up should be a primary consideration for SRMs in elderly and/or infirm patients with multiple comorbidities that would make them high risk for intervention and in those with limited life expectancy [25,28] [60]. Delayed intervention of more than 1 year after diagnosis does not seem to exacerbate the prognosis for later metastatic RCC [25,40,61].

Before enrolling a patient in an AS protocol an adequate renal tumour mass biopsy should be considered. In some cases a benign tumour will be shown while mostly the biopsy will confirm malignancy and this will be helpful to further define follow-up [48]. The patient should be counselled about the small but non-negligible risk of tumour progression during the AS period, possible loss of opportunity for NSS, lack of curative salvage therapies if metastatic disease were to develop, limitations of renal mass biopsy, lack of long-term data on surveillance, close follow-up imaging and required compliance.

For follow-up during the surveillance period, Rendon et al suggested CT or MRI every 3 months in the first year, every 6 months in the next two years and every year thereafter [23]. This high number of CTs was considered necessary to assure a safe surveillance strategy. However, in this regard, the recognized risk of radiation exposure due to multiple CT scans should be kept in mind. The optimum protocol and imaging modality is unknown at present but ultrasound, with or without contrast, may provide adequate images for measurement.

6. CONCLUSIONS

Not all SRMs are RCC. If untreated, the majority grows slowly and have low rate of progression to metastasis, at least in the initial years. ***At this time, an initial period of AS with regular imaging follow-up should only be considered for patients with SRMs < 4 cm who are considered unfit for intervention or have limited life expectancy or refuse treatment [62] (Grade C). Delayed intervention should be undertaken in tumours that show fast growth during AS and therefore may have a higher risk of progression to metastatic disease (Grade C).*** At this time, the whole body of literature is insufficient to recommend or disregard biopsy for SRMs. The identification of clinical, imaging and molecular markers of disease progression, as well as further research on the role of biopsy is needed to improve the selection of patients for AS. Until reliable prognostic parameters are formally identified, one must recognize that there is a small but non-negligible risk of developing metastatic disease in patients with SRMs followed expectantly.

Surveillance requires excellent patient compliance and rigorous follow-up with contrast enhanced CT or MRI. Finally, the long-term results of prospective AS studies such as the ongoing multicentre Canadian trial are eagerly awaited to more precisely identify the role of AS in the treatment of localized renal RCC. Molecular studies of prognostic factors for progression are in progress [39].

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IV. RADICAL NEPHRECTOMY FOR LOCALIZED RCC

1. INTRODUCTION

Radical nephrectomy (RN) includes the removal of the tumour-bearing kidney and has been the traditional approach for treating localized RCC in patients with a normal contralateral kidney [1]. Nowadays it is still the treatment of choice with excellent oncologic efficacy when the tumour is not amenable to NSS. Adrenalectomy and regional lymphadenectomy may be performed at the time of RN, but their benefit in absence of radiological signs of tumour invasion or in growth has not been proven in prospective randomised studies and consequently no hard recommendation can be made to this respect. According to a recent systematic review adrenalectomy should only be considered in select cases in which there are risk factors for adrenal involvement such as increased size and T stage, multifocality, upper pole location and venous thrombosis [2]. Lymphadenectomy is only desirable in the presence of enlarged lymph nodes on preoperative imaging and can increase survival when combined with adjuvant immunotherapy [3,4]. The randomised EORTC trial 30881 including 732 patients with preoperatively staged N0M0 tumours does show that lymph-node dissection combined with RN does not increase morbidity or mortality, but a survival advantage could not be demonstrated. This is mainly due to the low incidence of lymph-node metastases (4%) detected by lymphadenectomy. If RN is truly indicated, for instance for patients with locally advanced disease, a limited regional lymph node dissection still seems reasonable. There are reports that the removal of lymph nodes containing microscopic metastases may be beneficial to some patients [3].

2. FACTORS THAT AFFECT THE STATUS OF RN AS GOLD STANDARD FOR TREATING RCC

During the last decade, the status of RN has been called into question because of several factors including: a) equal oncologic efficacy as partial nephrectomy (PN) for renal tumours < 4 cm [5,6] and tumours between 4 and 7 cm [7,8], b) increased incidental detection of small (< 4 cm) renal masses with a significant proportion of benign tumours (up to 20%) (9-14), c) possibility of late recurrence of RCC in the contralateral kidney, d) a higher risk of chronic kidney disease (CKD) following RN [5,15,16].

Preservation of renal function is increasingly prioritized in the management of small renal masses and underscores the use of nephron-sparing modalities whenever feasible. Compared to patients

undergoing PN, patients undergoing RN were more likely to have proteinuria and CKD (defined by a serum creatinine level > 2.0 mg/dl) during follow-up [5,15]. This finding was later confirmed by the glomerular filtration rate (eGFR) estimated with the abbreviated Modification of Diet in Renal Disease Study equation (16-18). Of the patients with SRMs 26% had pre-existing CKD (GFR < 60 mL/min per 1.73 m²) before surgery. After surgery, the 3-year probability of freedom from new-onset CKD (GFR < 60 mL/min per 1.73 m²) was 80% after PN and 35% after RN. Corresponding values for the 3-year probability of freedom of moderate CKD (GFR < 45 mL/min per 1.73 m²) were 95% after PN and only 64% after RN. RN remained a significant risk factor for the development of new-onset CKD even after controlling for potential confounding factors such as hypertension and diabetes. RN might no longer be regarded as the gold standard treatment for small renal tumours and should be reserved for patients with massive renal tumours in whom PN is not an option [16,17,19]. In a recently published prospective study by Clark et al the postoperative change in creatinine clearance was significantly less ($P < 0.0001$) in the PN group (-0.09mL/s, -6.1%) compared to the RN group (-0.56mL/s, -31.6%). The authors state that the best method for evaluating global renal function is the 24-hours creatinine clearance [20].

RN is now recognized as a risk factor for the development of CKD, which is known to increase the risk of cardiovascular events and all-cause mortality [21]. This is an important issue as renal tumour patients often are elderly patients with multiple comorbidities such as hypertension, diabetes, and peripheral vascular disease that might lead to deterioration of baseline renal function. Therefore RCC patients undergoing nephrectomy cannot be compared to a healthy kidney donor population where the occurrence of CKD is exceptional [16,22-24]. Thompson et al compared overall survival (OS) in patients with localized RCC of 4 cm or less and normal contralateral kidney who were treated with RN and PN. Compared with PN, RN was associated with decreased OS in young patients (< 65 years) with SRMs [25].

Relative to PN, RN is associated with an increase in overall mortality and non-cancer-related death rate in patients with T1a RCC. Therefore, PN should be performed whenever technically feasible [26].

3. OPEN RADICAL NEPHRECTOMY

Open radical nephrectomy (ORN) can be performed by a transperitoneal or extraperitoneal approach. The choice of the surgical access depends on the size and position of the tumour, the patient's habitus and the surgeon's preferences. (Fig. 2, 3)

Indications for ORN include locally advanced renal tumours with invasion in the perirenal fat and

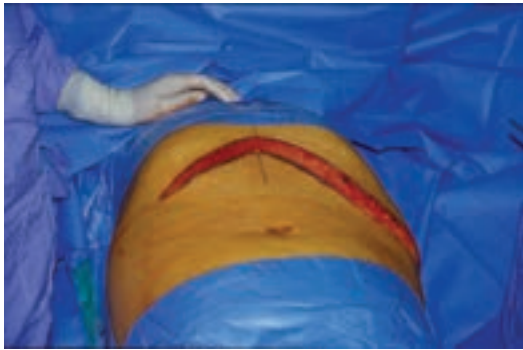


Fig. 2a: Left hemi-chevron incision for radical nephrectomy

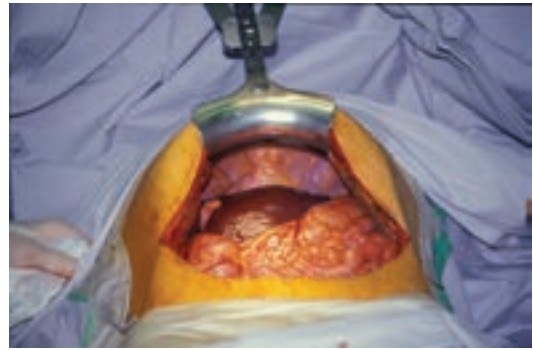


Fig. 2b: Chevron exposure of the upper abdomen



Fig. 3: Planning of a thoraco-phreno-laparotomy for larger upper pole tumors

adrenal gland (T3a), invasion in the vena renalis or vena cava (T3b and c), tumours that extend in the adjacent organs (T4) and probably also those tumours that will undergo an extensive large lymph node dissection [27]. (**Fig. 4**)

In a prospective randomised EORTC phase III study, Van Poppel et al found a perioperative blood loss < 0.5 l ($P < 0.001$) and severe hemorrhage (> 1 l) in 96.0% and 1.2% of patients with small renal tumours (≤ 5 cm) treated with ORN. Pleural damage and spleen damage were respectively seen in 9.3% and 0.4% of ORN patients [11]. Blom et al reported that lymph node dissection had no impact on the complication rate. The most common adverse events in patients treated with ORN without and with lymph node dissection, respectively were bleeding (6.5% vs. 9.4%), pleural damage (5.1% vs. 4.4%) and infection (5.7% vs. 5.2%). Less common adverse events were bowel damage, embolism and lymph fluid drainage [3].

In recent long-term retrospective comparisons between ORN, laparoscopic radical nephrectomy (LRN) and hand-assisted LRN (HALRN) for T1 and T2 renal tumours, the 5-year disease-free survival, CSS and OS for ORN were similar at 90%, 93% and 87%, respectively (28-32). Laparoscopic approaches have shown similarly favourable results. The postoperative complication rate for ORN was



Fig. 4a: View after left radical nephrectomy and extended lymphadenectomy



Fig. 4b: Extended lymphadenectomy for rightsided RCC, comprising the pericaval, inter-aorto-caval and pre-aortic nodes

acceptably low (9.8%) [28-32]. The most common immediate complication is secondary hemorrhage [33].

4. LAPAROSCOPIC RADICAL NEPHRECTOMY

a) Introduction

Many still consider LRN the gold standard for the surgical management of T1 and T2 tumours as safety, survival rate and non-recurrence rate are not significantly different from those associated with ORN. Today, however the majority of T1a and some T1b tumours are more properly treated with nephron-sparing techniques [32].

b) Indications

Currently, LRN is best indicated for the surgical management of T1-2N0M0 tumours that warrant complete removal of the kidney [32]. However, when performed in advanced laparoscopic centres by significantly experienced surgeons, this can be broadened to include more extensive masses [28,34-36]. Mattar et al summarized the expanding indications for LRN, including very large tumours, locally advanced disease, renal vein thrombi and cytoreductive surgery [37].

c) Oncologic outcome

Hemal et al evaluated the oncologic outcome of 132 cases of LRN with intact specimen removal for T1-2N0M0 RCC. The 5-year CSS in patients with a pT1a, pT1b and pT2 tumour was 97.2, 86.3 and 82.2%, respectively (significantly lower in pT2 than pT1a, $P = 0.008$). The 5-year recurrence-free survival in patients with a pT1a, pT1b and pT2 tumour was 97.2, 84.3 and 82.2%, respectively (significantly lower in pT2 than pT1a, $P = 0.02$) [38]. Another study demonstrated that the efficacy and oncological outcome of LRN in elderly patients (≥ 70 years) was as promising as those in their younger counterparts (< 70 years) [39]. More recently in 2009, Berger et al presented long-term, mean 11.2 years follow-up, in 73 patients undergoing LRN for pathologically-confirmed RCC prior to 1999. All patients had completed a minimum of 10-year follow-up since surgery (range, 10-15 years). Actual 10-year overall, cancer-specific and recurrence-free survival rates were 65%, 92%, 86%, respectively. Twelve-year overall, cancer-specific and recurrence-free survival rates were 35%, 78%, 77%, respectively. At a mean 67 months, 10 patients (14%) developed metastatic disease, of whom 8 (11%) died. The authors concluded that long-term oncological outcomes after LRN for RCC are excellent and appear comparable to open surgery [40].

d) Complications

The incidence of complications associated with LRN

ranges from approximately 10 to 20%, and does not significantly differ from that associated with open surgery [36,41]. Compared with the open approach, LRN is associated with significantly less blood loss [41,42], significantly lower dose of analgesic agents during the postoperative course [36,42] and significantly shorter hospital stay [41,42]. A recent retrospective chart analysis by Permpongsol including 549 patients reported total and major complication rates after LRN of 20% and 7.3%, respectively. Intra- and postoperative complication rates were 6.6% and 13.8%, respectively. The most common complications were related to injury of the adjacent organs (2.37%) or the diaphragm (0.73%). The second most commonly identified complications were vascular complications (2.2%) [43]. One of the most important steps during LRN is the control of the hilum [44]. Open conversions occurred in 2.9% of cases [43].

Gong et al compared LRN in patients with T1 ($n=98$) and T2 renal tumours ($n=43$). Transfusion rates (8% vs 23%) and open conversions (1% vs 12%) were higher for T2 lesions while postoperative complication rates (25% vs 21%) and hospital stay (2.8 vs 2.4 days) were similar between both groups. Complication rates were higher than in other series, which may have been due to the patient population and the cautious reporting [45]. The incidence of major complications unique to LRN and number of conversions decreases with surgeon's experience. Some authors report a minimum experience of 50 procedures is necessary for reducing the risk of major complications [46,47]. Mentoring the surgeon is an effective approach for safely introducing minimally invasive surgery such as LRN into practice [46,48,49].

e) Comparison of different approaches

Two prospective randomized studies comparing transperitoneal LRN and retroperitoneal LRN found a shorter operative time for the retroperitoneal method. Both approaches are similar in terms of other patient outcomes and complications [50,51]. In a retrospective study no significant differences in the two approaches were found [52]. Berglund et al found a trend favouring the retroperitoneal approach for LRN in the morbidly obese patient [53].

f) LRN versus ORN

Portis et al compared LRN and ORN for localized RCC and reported no significant differences in oncologic outcome between the two procedures [54]. Recently, Burgess et al performed the first randomized controlled trial comparing LRN and ORN. Maximum tumour size was 8 cm and groups were well matched between the 45 patients. No significant differences were observed in blood loss, mortality rate, operation-room time and hospital stay. The only significant differences were less postoperative pain and faster return to normal activities in the LRN

group [55]. A long-term prospective comparison of LRN and ORN for T2 tumours showed that there was no difference in 5-year survival and that patients treated with LRN experienced significantly less blood loss, had a decreased analgesic requirement, shorter hospital stay and more rapid convalescence [28]. A comparison of the 5- and 10-year disease-free survival, CSS and OS of patients with T1 and T2 renal tumours treated with transperitoneal LRN or ORN revealed no significant differences [56].

g) Purely LRN versus hand-assisted LRN (HALRN) versus ORN

Matin et al retrospectively reviewed 271 patients that underwent HALRN or transperitoneal purely LRN. The operative time was shorter for HALRN than for LRN but HALRN was associated with greater use of analgesia and longer hospitalization [57]. Montgomery et al found that wound infections and port-site hernias occurred less frequently with HALRN than with ORN, but more often than with LRN [58]. Five recent long-term retrospective studies including 647 patients with a mean follow-up of almost 4 years for the laparoscopic cohort compared LRN (pure LRN or HALRN) with ORN for T1-2 lesions. The rate of postoperative complications for LRN and ORN was similar and low. LRN was superior to ORN in terms of hospital stay and convalescence time. The oncologic outcome was similar for both treatment groups [28-32]. Local recurrence rates were low and most studies had none, particularly in patients with less than T3 disease. Furthermore, there were no port-site metastases [32,59] [28-31]. A recent study analyzing 255 LRN showed that approach (standard vs. hand assisted) and specimen handling (morcellation vs. intact extraction) has no discernible impact on oncological perioperative and long-term outcomes after LRN [60].

We can conclude that several comparisons support the superiority of LRN over ORN for the majority of renal tumours. Oncologic control is similar, morbidity is low and does not significantly differ from open surgery, and convalescence time is shorter after LRN.

5. ROBOTIC RADICAL NEPHRECTOMY

Hemal et al prospectively compared the feasibility and safety of LRN and robotic RN for localized renal tumours (T1-2N0M0). Both groups had comparable oncological and operative outcomes. Robotic RN was associated with longer operative time and increased cost. There were no remarkable advantages of robotic RN observed over LRN [61].

6. FOLLOW-UP AFTER RADICAL NEPHRECTOMY

Skolarikos et al published a comprehensive review of the evidence supporting the necessity for follow-up strategies for RCC after nephrectomy [62]. The rationale for postoperative surveillance of

patients with RCC is to monitor for post-operative complications, renal function, local recurrence, recurrence in the contralateral kidney and metastatic disease in order to allow for appropriate treatment. No consensus currently exists on surveillance guidelines after surgical extirpation of RCC. Publications on postoperative surveillance are based on retrospective studies. The intensity and type of surveillance should be established according to the risk of recurrence and metastasis. Leibovich et al developed a scoring system based on tumour stage, regional lymph node status, tumour size, nuclear grade, and histologic tumour necrosis to predict disease progression after RN for patients with clinically localized clear cell RCC [63]. Recently, Kassouf et al published Canadian guidelines for surveillance after nephrectomy for non metastatic RCC, based on pathological stage [64]. Grades of recommendations are provided using the modified Oxford Centre for Evidence-based Medicine scheme. Recommended surveillance after RN of pT1 tumours includes medical history and physical examination, blood biochemical tests, and chest-X-ray every year. Abdominal CT is recommended at 24 and 60 months (Grade C). Recommended surveillance after RN of pT2 tumours includes medical history and physical examination, blood biochemical tests, and chest-X-ray every 6 months for 3 years then yearly. Abdominal CT is recommended at 12, 36, 60, 84 and 108 months (Grade C) [64]. Most contemporary surveillance protocols have been based on stage alone [64]. Recently, Siddiqui et al presented a subtype-specific multifactorial surveillance protocol based on various pathological features that have a significant effect on recurrence. This surveillance protocol seems to be better than those based on tumour stage alone and can be used to efficiently adapt postoperative imaging to the individual patient [65]. The addition of molecular predictors may identify those patients at high risk of progression in which the follow-up protocol will be more intensive [66].

7. CONCLUSIONS

RN is no longer the gold standard treatment for small renal tumours. RN as management for clinically localized RCC should be limited to those cases where the tumour is not amenable to nephron-sparing surgery. ***Routine extended lymph node dissection in patients with detectable lymph nodes does not improve survival and can be restricted to staging purposes (Grade A). Adrenalectomy should only be considered in selected cases in which there are risk factors for adrenal involvement (Grade B).*** The choice of the transperitoneal or peritoneal approach has no impact on the efficiency and safety of the LRN procedure. LRN is reserved for stage T1 and T2 tumours without strict limitations for tumour size. Complications are mainly vascular of type and are low in the hands of an experienced surgeon. There are no significant differences in oncological

outcome between LRN and ORN. **However, LRN has benefits over ORN in terms of morbidity. Therefore, LRN should be the standard of care for T1 and T2 tumours, provided that it is performed in an advanced laparoscopic centre by an experienced surgeon and NSS is not applicable (Grade B).** No consensus currently exists on surveillance guidelines after surgical excision of RCC. The majority of follow-up strategies after RN is currently based on tumour stage alone, but tends to include more histological prognostic factors in the future to tailor surveillance to the individual patient.

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V. PARTIAL NEPHRECTOMY

1. INTRODUCTION

Partial nephrectomy (PN) includes the complete removal of a localized renal tumour while maintaining as much normal renal parenchyma as possible. Advantages of PN are the preservation of renal function, the prevention of Chronic Kidney Disease (CKD) and the avoidance of overtreatment of benign renal masses. PN in solitary kidneys with limited ischemia time results in minimal changes in long-term renal function [1]. Moreover, some studies show a better quality of life after PN than after RN [2,3].

2. CONCERNS WITH THE USE OF PARTIAL NEPHRECTOMY

a) Risk of recurrence – positive surgical margins

Significant concern with the use of PN for treating RCC is the risk of local recurrence in the ipsilateral kidney due to incomplete resection. This concern may be tempered by the low rates of recurrence following PN in the literature (0% to 10%) and even lower recurrence rates (1% to 3%) when performing PN for tumours < 4 cm [4]. Moreover many "local recurrences" are not due to incomplete removal but are rather de novo tumours, such as multifocal papillary RCC.

Analyses of the available literature reveals that frozen sections or final pathologic examination of the margins have minimal clinical significance and that a normal tissue margin of just 1 mm may be

sufficient to prevent local recurrence and disease progression from RCC. Margin status is more important than margin size though a positive surgical margin does not always result in local recurrence and/or disease progression. Therefore surgeons should be aware that not all patients with positive surgical margins on final pathology need to undergo second surgery immediately. These patients can be judiciously followed with periodic ultrasound and CT scan to monitor their higher risk of local recurrence (and disease progression) [5]. There are three recent reports from one centre on pure enucleation, meaning that the margin size was 0.00 mm. Simple enucleation of the tumour relying on the presence of an intact tumoural pseudocapsule was shown to be safe. Only 2 of the 107 patients developed a local recurrence (1.9%) after simple enucleation of the tumour, one locally and one associated with distant metastasis [6]. One year later the same group found no local recurrence at the level of the enucleation site and three had a kidney recurrence elsewhere in the kidney after pure enucleation of the tumour in 232 patients. Kidney recurrence was most likely attributable to multifocality [7]. Another study reported two local recurrences with simultaneous metastatic progression and one kidney recurrence elsewhere in the kidney after simple enucleation for pT1b tumours [8]. A recent histopathological study showed that if there is pseudocapsule invasion into normal parenchyma, the presence of a thin layer of tissue can justify the presence of negative surgical margins even if a simple tumour enucleation is performed [9].

A survey on the use of LPN in 17 centres (n= 855 cases) in the United States and Europe revealed that 21 (2.4%) cases had positive surgical margins [10]. Permpongkosol et al identified a positive margin in 9 of the 511 patients (1.8%) undergoing LPN [11]. Frank et al found a similar surgical margin rate in patients that underwent a LPN for central and peripheral tumours [12]. Positive margin rate was 6.7% in solitary kidneys [13]. Lam et al recently reported that the rates of positive margins in PN specimen could be reduced with an optimal visualization of the tumour and the tumour margins. This could be achieved by intraoperative use of ultrasound for deeper tumours, cold-scissor parenchymal transection, embolization, and hilar clamping [14]. Currently, there is controversy on the optimal management of a positive surgical margin. For a large ("extensive") positive margin it seems logical that additional surgery should be advised, either repeat PN (primary or secondary, open or laparoscopic), or in the appropriate patient, an RN [11,15]. However, recent data indicate that positive surgical margins after a completely deemed resection at the time of PN were not associated with an increased risk of local recurrence or metastatic disease. Therefore it has been suggested that select patients with microscopic ("focal") positive margins

can be safely offered close long-term surveillance without compromising oncologic control [15,16]. While these data demonstrate that patients with a pathologically positive margin may be observed, negative surgical margins should always be the goal in any oncologic procedure, including PN. Very recently, Bernhard et al identified three independent predictive factors for ipsilateral recurrence following NSS in RCC: tumour size > 4 cm, tumour bilaterality (synchronous or asynchronous) and positive surgical margins status (hazard ratios were 6.31, 4.57 and 1.15, respectively). Among the 809 NSS procedures with a medium follow-up of 27 months (1-252 months) 25 ipsilateral recurrences (3.2%) occurred at a median time of 27 (14.5 – 38.2) months. Positive surgical margins occurred in only 1.5% of the patients. The authors concluded that a prolonged follow-up should be recommended in patients presenting one or more of the three identified factors. The main limitation of the study was its retrospective nature and a short follow-up (median FU, 27 months) [17]. A previous retrospective study including data from 26 institutions in Europe and the United States analyzed the outcome of 111 patients with positive surgical margins following NSS. Positive surgical margins status occurred more frequently in the imperative group and is associated with an increased risk of recurrence, but margin status was not an independent predictor of both cancer-specific and overall survival [18]. These data taken together suggest that identified predictive factors for local recurrence after NSS do not necessarily affect survival and should not prohibit NSS in that setting. A recent study that reviewed the clinical records of 114 NSS procedures found a positive surgical margin rate of 1.75%. No disease progression or RCC attributable deaths were associated with positive surgical margins. These findings suggest that total nephrectomy should be avoided as a response to positive surgical margins [19].

b) Hilar clamping - warm and cold ischemia time – renal function – hemostatic agents

During the development phase there have been initial concerns with the use of LPN as related to a somewhat longer warm ischemia time and increased risk of major postoperative complications such as urinary leakage and hemorrhage [20]. Therefore the decision to perform an OPN or LPN depends on the experience of the individual laparoscopic surgeon. OPN is most often done through a lumbotomy, after exposure of the kidney and the tumour with its overlying fat. (Fig. 5,6) With increasing experience, LPN is now being performed at a growing number of tertiary centres worldwide. The technical challenge is to completely resect the tumour in a bloodless field followed by hemostatic renorrhaphy within a limited warm ischemia time. Factors associated with superior outcomes of LPN are routine hilar clamping,

adjunctive use of hemostatic agents and renal parenchymal closure by suture ligation [21].

Hilar clamping minimizes blood loss and allows precise tumour excision and renal reconstruction in a nearly bloodless field. Today, there is no consensus about the clamping technique to be employed (artery only versus artery & vein) [22].

Very recently, Huber et al evaluated bleeding complications after open NSS in 196 patients at their institution (from 2005 to 2008). Median tumour diameter was 2.7 cm (range 0.5 – 11.8 cm). Bleeding required conservative (six), interventional (six) or surgical (three) therapy in 15 of the 196 cases (8%). The authors identified multifocality ($P=0.039$) and imperative indications ($P=0.043$) as risk factors for hemorrhage after NSS. The management of bleeding was very successful, relying on transarterial embolization (TAE) as an effective and safe treatment. In rare cases of severe bleeding surgical exploration is unavoidable, with a lower chance of kidney preservation [23].

A recent well-designed but small prospective study has investigated separate renal function with effective renal plasma flow and renal parenchymal volume measured from CT scan. The authors could demonstrate that 25 min of warm ischemia time (WIT) is a cut-off for irreversible renal damage [24]. A recent large multi-institutional study has evaluated



Fig. 5: Installation for lumbotomy



Fig. 6a: Exposure of the kidney in a lumbotomy after complete hilar dissection

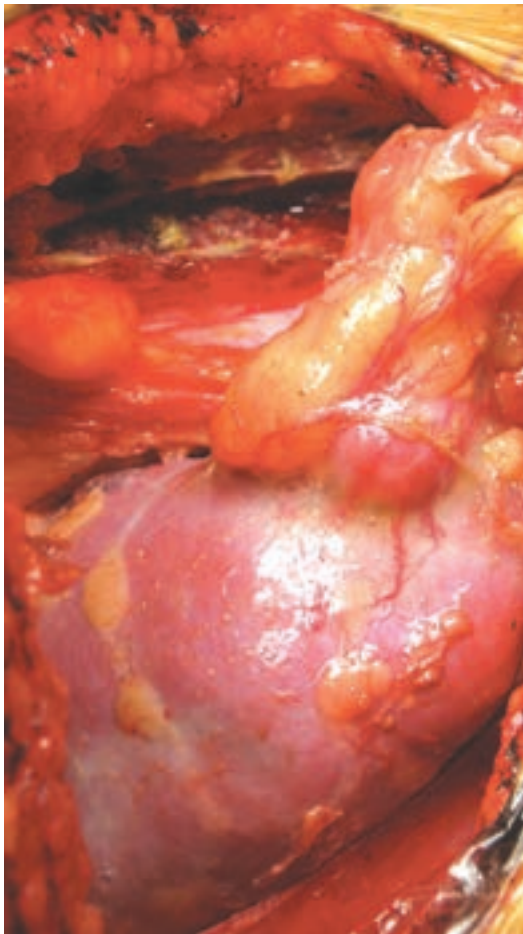


Fig. 6c: Freeing the kidney and the tumor, covered by peri-renal fat

the renal effects of ischemia in patients with solitary kidneys undergoing open NSS. The authors concluded that when vascular clamping during open NSS is necessary efforts should be made to limit WIT to 20 minutes and cold ischemia to 35 minutes in order to avoid an increased risk of chronic renal insufficiency and acute renal failure [25]. The currently recommended WIT is 20 minutes or less,



Fig. 6b: Complete mobilization of the tumor bearing kidney on its artery, vein and ureter

regardless of surgical approach. If a longer ischemia time is anticipated, cold ischemia should be instituted up front at the start of PN. Cold ischemia with ice slush [26] should be kept as short as possible, ideally within 35 min [27]. After surface cooling of the kidney by ice slush for about 10 minutes, the kidney can be clamped, and a safe cold ischemia time for a maximum of 35 min has been described in several studies [13,25,28,29]. Other methods to induce cold ischemia are arterial and ureteral perfusion [30-33]. Recently, an early unclamping technique has been suggested by which only the initial parenchymal suturing is performed with the hilum clamped while sutured renorrhaphy is performed in the unclamped, revascularized kidney. This resulted in a reduction of WIT by more than 50% (13.9 vs. 31 min, $p < 0.0001$). Postoperative hemorrhage and reoperation also tended to be lower but was not statistically significant. The current mean WIT < 14 minutes is lower than or similar to that in contemporary OPN series [34]. Other authors have confirmed these findings [35-37]. Nevertheless, the safe maximum duration of WIT remains in debate.

A recent study evaluated the impact of WIT on renal function in 101 LPN patients using the Modification of Diet in Renal Disease (MDRD) equation to determine eGFR. The study results indicated that clinically significant risk for postoperative renal function impairment is evident only at a WIT of > 40 minutes. Incidence of renal function impairment was more than 2-fold higher in patients with WIT > 40 minutes than in the other groups ($p = 0.077$). Larger studies in populations with normal preoperative renal function and with various degrees of CKD are required to clarify the risk factors for postoperative renal function impairment, including WIT. In the meantime every attempt should be made to reduce WIT [38].

Another study revealed that greater tumour size, central tumour location and higher body mass index are associated with longer WIT. By including these 3 factors into a nomogram prolonged WIT (> 30 minutes) may be predicted before surgery [39]. However, the experience of the surgeon may be the most critical parameter.

Very recently, Chan et al retrospectively evaluated in 65 patients (35 OPN and 30 LPN) which clinical parameters, alone or jointly, accurately predicted unilateral renal function after OPN and LPN. In the univariate regression analysis, intraoperative visually estimated preserved renal parenchyma ($P<0.001$), tumour size (radiologic, $P=0.017$; pathologic, $P=0.041$) and procedure type (laparoscopic vs. open) ($P=0.021$) were the only factors found to be significantly correlated with postoperative scintigraphic differential renal function. Tumour depth ($P=0.050$) was borderline significantly correlated with postoperative scintigraphic differential renal function. Intraoperative visual estimation of preserved renal parenchyma volume was the most accurate predictor of actual postoperative unilateral renal function and should be routinely documented during OPN and LPN [40].

The use of hemostatic agents and glues during LPN in 18 centres ($n=1347$ cases) in the United States and Europe was shown to be routine in most centres performing LPN (in 77.4%). The rates of postoperative hemorrhage requiring transfusion and urine leakage rates were low in this survey (2.7% and 1.9%, respectively) [41].

c) Long-term oncologic data – risk of complications

A randomised prospective phase III trial was conducted (EORTC 30904) comparing OPN and ORN in 541 patients with tumours ≤ 5 cm and a normal contralateral kidney. Van Poppel et al concluded that the complication rate with OPN is slightly higher than with ORN [42]. The long-term oncological results are not tractable.

Porpiglia et al retrospectively analyzed 90 LPN procedures. The only variable that was found to correlate with a significantly higher rate of complications was a corticomedullary tumour growth pattern as opposed to a cortical growth pattern ($P=0.02$). It has to be noted that this finding is based on univariate analysis (no multivariate analysis was performed). To reduce the risk of complications associated with LPN the authors recommended selection of patients with cortical renal lesions only [43]. More recently, Turna et al retrospectively analyzed 507 LPN procedures. Presence of a solitary kidney, prolonged WIT and increased intraoperative blood loss were found to be independent risk factors on multivariate analysis for the development of postoperative complications after LPN [44]. Probably the new categorization as proposed by Ficarra et al and Kutikov et al will be helpful in defining risk factors [45,46].

3. OPEN PARTIAL NEPHRECTOMY

a) Introduction

Open partial nephrectomy (OPN) is the nephron-

sparing modality with the largest clinical experience and the longest follow-up. OPN continues to be the treatment of choice for the management of localized RCC given its wide application over the last two decades and the most substantial supporting body of operative and oncologic data. Importantly, unlike ablative treatment options OPN allows definitive pathological identification (i.e. stage, grade and histology) and proof of complete resection. Essential surgical principles include excellent exposure, control of the renal vasculature, careful excision of the tumour with a negative surgical margin and repair of the parenchymal defect and collecting system to minimize the risk of postoperative hemorrhage or urinary fistula. (Fig. 7,8)

b) Indications

The standard indications for NSS according to the EAU guidelines are divided in the following categories:

- absolute (anatomical or functional solitary kidney)
- relative (functioning opposite kidney that is affected by a condition that might impair renal function in the future)
- elective (localized unilateral RCC with a healthy contralateral kidney)

Relative indications also include patients with hereditary forms of RCC, who are at high risk of developing a tumour in the contralateral kidney in the future [47]. Since more SRMs are detected now, elective PN has been adopted more frequently for the treatment of such tumours. During the last decade elective PN has become the gold standard for the treatment of T1a tumours (<4 cm) in patients with a normal contralateral kidney [48,49]. When PN is performed in carefully selected patients in specialized centres, indications can be expanded to include T1b tumours (4–7 cm) [50–61]. (Fig. 9,10) Also multifocal tumours can be dealt with (Fig. 11) as well as centrally located tumours that can need intraoperative ultrasound to localize tumours completely covered by healthy parenchyma. (Fig. 12)

c) Oncological outcome

Lee et al compared RN and OPN for tumours <4 cm and found equivalent oncological results at 5-years (disease-free survival of 96%) with no local recurrences [48]. Table 1 presents the oncologic outcome of large series of nephron-sparing surgery [48–50,58,62–73]. PN for RCC <4 cm (T1a) is now established standard. More recently, PN is being proposed for T1b RCC (4–7 cm). Several recent studies indicate that elective PN can achieve similar oncological outcomes as RN for select T1b tumours [50,54,55,57,59,61]. Table 2 presents studies assessing the oncologic outcome following NSS in

Table 1. Oncologic outcomes of large series of NSS

Author	No . of patients	Mean tumour size (cm)	5-yr CSS (%)	10-y CSS (%)	Local recurrence (%)	Mean follow-up (mo)
Steinbach et al (62)	121	5.5	90	-	4.1	40
Moll et al (63)	142	4.5	98	-	1.4	35
Lerner et al (64)	185	4.1	89	77	5.9	44
Belldegrun et al (65)	146	3.6	93	-	2.7	74
Herr et al (66)	70	3.0	-	97	1.4	120
Hafez et al (119)	485	3.4	92	-	3.2	47
Lee et al (48)	79	2.5	95	-	0	40
Lau et al (67)	164	3.3	98	-	3	41
Filipas et al (68)	180	3.3	98	-	1.6	56
Delakas et al (69)	118	3.4	97.3	96.4	3.9	102
Patard et al (50)	314	2.5	97.8	-	0.8	62.5
Fergany et al (70)	400°	4.2	89	82	3.5	44
Becker et al (58)	241	3.7	97.8	95.8	1.4	66
Pahernik et al (71)	715	3.0	98.5	96.7	3.3	81
Pahernik et al (72)	103°	4.2	89.6	76	0.1	96
Van Poppel et al (73)	51	3.0	98.0	-	0.0	78

° solitary kidney

CSS: cancer-specific survival

Reprinted from Van Poppel H. Efficacy and safety of nephron-sparing surgery. Int. J Urol, 2010;17(4):314-26.

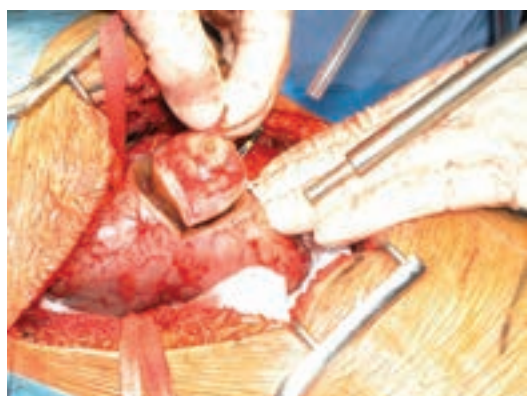


Fig. 7a: Wedge resection after bulldog clamping of both artery and vein

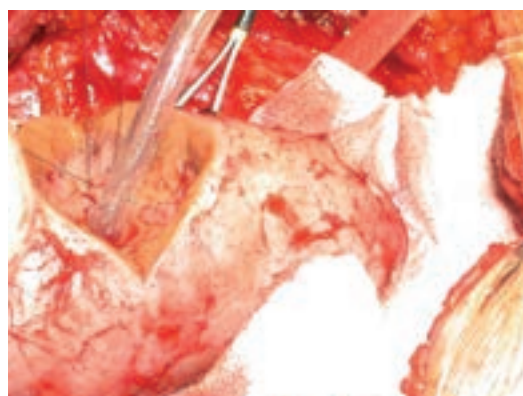


Fig. 7b: Oversewing of small arteries and veins



Fig. 7c: Closure with single approximating sutures

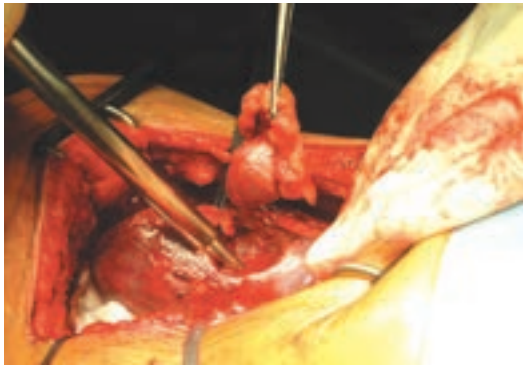


Fig. 8a: Open enucleoresection of a small RCC with a rim of healthy parenchyma



Fig. 8b: Application of hemostatic adhesive agent (Tachosil)



Fig. 9a: Exposure of RCC at renal hilus



Fig. 9b: Reconstruction of the kidney after midpolar tumorectomy



Fig. 9c: Reconstruction after midpolar resection

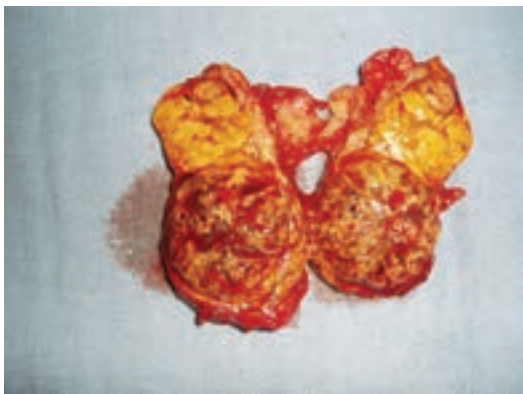


Fig. 10a: Upperpole RCC with en bloc adrenalectomy with small metastasis



Fig. 10b: After upper pole amputation and adrenalectomy and lymph node dissection for T3a RCC



Fig. 11a: One large and multiple small papillary type I RCC's

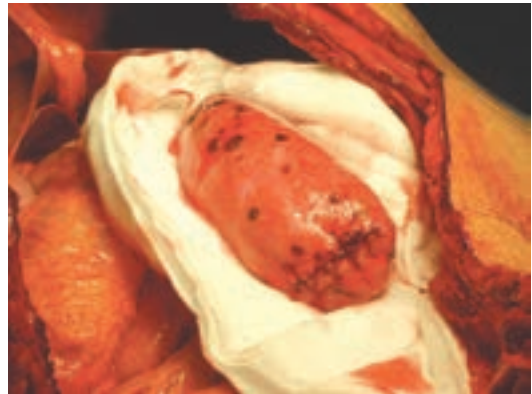


Fig. 11b: After resection of the larger, and thermoablation of the smaller lesions



Fig. 12a: Intra-operative ultrasound for intra-renal RCC

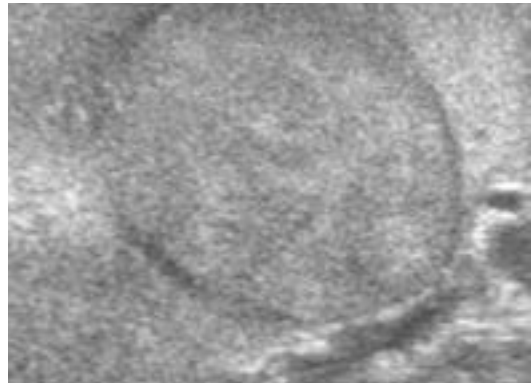


Fig. 12b: Intra-operative ultrasound to detect an intraparenchymal tumor

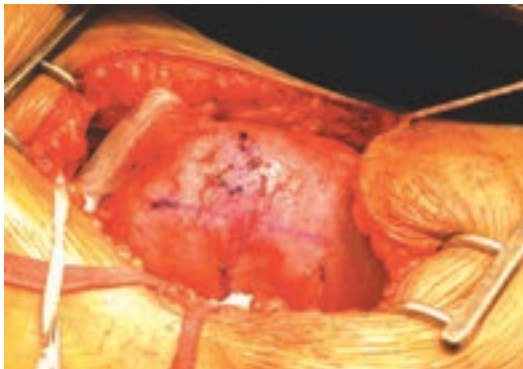


Fig. 12c: US localization of the intra-renal tumor



Fig. 12d: Resection of overlying renal cortex



Fig. 12e: Enucleation of deep intrarenal mass

relation to tumour size > 4 cm or ≤ 4 cm [8,50,54, 55,57,58,60,74]. Pahernik et al recently compared PN for pT1a (≤ 4 cm) and pT1b tumours (4-7 cm) in 474 PN procedures; estimated CSS was 97.9% and 95.8% at 5 years, and 94.9% and 95.8% at 10 years. This study failed to demonstrate statistical significant differences in terms of CSS after PN for T1a and T1b tumours [75]. This was also observed in a recent multicentre study of Patard et al [56]. Crispin et al recently reported durable cancer control in 798 patients undergoing PN for T1 renal tumours (≤ 7 cm). They found that overall, CSS, metastasis-free and local recurrence-free survival significantly decreased with each 1 cm increase in size in all tumours treated and in those with pathologically confirmed RCC [76]. A recent multi-institutional study revealed cancer control equivalence between RN and PN in patients with high-grade Fuhrman III-IV or with pT3a histology. Conversely, CSS after PN is statistically less than that after RN in patients with tumours > 7 cm. It has to be noted that only 29 of 925 patients (3.1%) with tumour size > 7 cm were treated with PN at 1 of 13 participating centres. Larger cohorts are required to confirm the results [77].

A recent study analysed the data of 1205 T1N0M0 RCC patients treated with NSS. Despite the suggested more aggressive phenotype of the papillary histologic subtype, the authors found no statistically significant differences in cancer-specific mortality among the papillary, chromophobe, and clear cell variants [78].

d) Complications

When performed in appropriate patients and in centres with sufficient expertise, OPN can offer for small renal tumours a perioperative morbidity profile similar to that of ORN. The rate of postoperative complications was 13.7% in a recent multicentre comparative study by Gill et al including 1029 patients with renal tumours (< 7 cm) that underwent OPN. The rate of postoperative hemorrhages and urologic complications was 1.6% and 5.0%, respectively. [28]. The best available evidence on this subject is the prospective randomised EORTC phase III trial which

compared the complications of elective PN and RN in patients with renal tumours ≤ 5 cm. In this study reported by Van Poppel, PN was associated with higher risk of severe perioperative bleeding (3.1% vs. 1.2%), reoperation due to side effects (4.4% vs. 2.4%) and having an abnormal postoperative CT scan (4.4% vs. 2.0%). The rate of urinary fistulas was 4.4% [42]. In a retrospective multicentre study, Patard et al demonstrated in 730 elective OPN procedures that perioperative morbidity as measured by blood loss, urinary fistula rate, and need for blood transfusion was significantly increased for tumours > 4 cm in diameter. They concluded that expanding the indications of elective OPN to larger tumours is associated with an increased but acceptable morbidity [56]. In addition, a recent study including 1117 PN revealed that 4.5 % of patients developed postoperative urinary fistula. Patients with tumours > 2.5 cm were 2-fold more likely to develop a urinary fistula compared to patients with tumours < 2.5 cm (P = 0.04) [79].

Renal failure is another complication of PN. A recent study analysed the data of 166 patients with pathological T1-3 N0M0 RCC treated with PN. The investigators identified perioperative blood loss, hilar clamp time and preoperative GFR as independent predictors of renal failure (decrease in GFR of >25%). It is possible that surgical experience could minimize the rate of renal failure especially in patients with pre-existing renal function impairment [80].

The risk of a significant complication may increase with the technical complexity of the case such as larger tumours or centrally located tumours. However, most complications can be managed conservatively and usually resolve without significant morbidity. Over the last years, surgical techniques have been improving and complication rates further decreasing with increasing surgical experience.

e) Comparison between PN and RN

McKiernan et al conducted a 10-year prospective study to compare 173 patients who underwent

Table 2. Studies assessing oncologic outcome following NSS in relation to tumour size > 4 or ≤ 4 cm

Author	No. of patients and pT stage	5-yr CSS (%)	10-yr CSS (%)	Local recurrence (%)	Metastasis (%)	Mean FU (mo)
Patard et al (50)	314 (pT1a)	97.8	-	0.8	2.4	51
	65 (pT1b)	93.8	-	3.6	7.1	62.5
Leibovich et al (55)	91 (30 pT1a, 60 pT1b, 1 pT3a)	98.3	-	5.5	4.4	106
Mitchell et al (74)	33 (21 pT1b, 12 pT3)	96.2	-	2.3	-	34
Carini et al (8)	71 (30 pT1a, 31 pT1b, 10 pT3)	85.1	-	4.5	14.9	74
Dash et al (57)	45 (41 pT1b and 4 pT3)	80	-	2.2	-	14
Becker et al (58)	69 (62 pT1b, 4 pT2, 3 pT3a)	100	100	5.8	5.8	74
Peycelon et al (60)	61 (42pT1b, 12pT2, 6 pT3a, 1 pT3b)	81	78	9.8	19.7	70.7
Joniau et al (54)	67 (13 pT1a, 49 pT1b, 1 pT2, 4 pT3a)	99	-	4.0	6.0	40.1

Reprinted from Van Poppel H. Efficacy and safety of nephron-sparing surgery. *Int. J Urol*, 2010;17(4):314-26.

RN with 117 patients who underwent PN for renal tumours ≤ 4 cm and a normal contralateral kidney. The incidence of risk factors for renal insufficiency did not differ between the two groups. After controlling for perioperative risk factors for renal failure, patients undergoing RN were at a greater risk of chronic renal insufficiency (creatinine ≥ 2.0 mg/dL) than a similar cohort of patients undergoing PN [81]. Moreover, in Dash et al prospective comparison of 196 patients undergoing PN and RN for T1b tumours, serum creatinine level at 3 months post-operative was significantly lower in the PN cohort [57].

Patard et al performed a retrospective analysis of 1454 patients undergoing PN or RN for T1N0M0 tumours. In patients treated by PN, the cancer death rate was higher for T1b tumours compared to T1a tumours (6.2% vs 2.2%, respectively). However, in the group of T1b tumours, there was no significant difference in the rate of cancer specific deaths whether treated with PN or RN (6.2% vs 9%, respectively). This study suggests that it is safe to expand the indications of PN to include patients with T1N0M0 tumours up to 7 cm [50]. Likewise, Leibovich et al performed a retrospective analysis of 932 patients undergoing PN or RN for T1b renal tumours. Their study included control groups of T1a tumours for each procedure. There was no statistically significant difference in survival at 5 years between patients treated with PN and RN after adjusting for important pathological features. This study also shows that PN for T1b (4 to 7 cm) RCC can result in excellent outcomes when performed in appropriately selected patients [55]. A recent study confirmed these results and suggested designing a prospective study to compare RN and PN in the management of RCC up to 7 cm [59]. Thompson et al combined data from the Mayo Clinic and Memorial Sloan Kettering Cancer Center of patients with 4 to 7 cm renal masses treated with RN (873) vs. PN (286). They suggest that OS and CSS are not compromised when PN is compared with RN for tumours up to 7 cm. This study adds considerable evidence supporting PN use when technically feasible [61]. A recent study represents the largest and the only population-based analysis of cancer control efficacy of NSS vs. RN in T1bN0M0 RCC. It used Surveillance, Epidemiology, and End Results (SEER) data where 275 NSS were matched with 1100 RN for T1bN0M0 RCC. It indicates that NSS does provide equivalent cancer control relative to RN. NSS should be considered equally effective to RN for T1bN0M0 RCC [82]. None of these studies were randomised like the EORTC 30904 trial comparing PN to RN for patients with RCC up to 5 cm of which the results are pending [42].

A recent analysis of the SEER-9 database revealed that relative to PN, RN predisposes to a rise in overall mortality and non-cancer related mortality rate in patients with T1aN0M0 RCC [83]. Convincing data show equivalence of PN and RN for cancer control and superiority of PN in terms of preserving renal

function, preventing CKD and subsequent long-term cardiac morbidity and mortality and improved overall survival [53,84]. Therefore, patients with T1 renal tumours should undergo PN whenever technically feasible. The expanding role of PN is the topic of a recent paper of European Urology [85]. A comparative population-based study analysed the rate of PN vs. RN for clinically localized RCC (SEER data 1989-2004). Of 19,733 assessable patients, 2,614 (13.2%) had PN and 17,119 (86.8%) had RN. The use of PN decreased with increasing tumour size and increasing age and increased with more contemporary years of surgery (all $P < 0.001$). Although the rate of PN use increased over time, unexplained variability remained. Regional and gender differences in PN rates represent findings that need to be urgently addressed and corrected. The PN rate was 16.4% in San Francisco-Oakland, vs. 7.6% in New Mexico ($P < 0.001$). Women were 10% less likely to have a PN than men. The study has several limitations. There was no information about surgical approach (open vs. laparoscopic vs. robotic) of PN or RN that was performed, tumour location, number of renal units and renal function. Information on comorbidity status, hospital type (academic vs. community), surgical training and expertise (years in practice) was also unavailable [86].

4. LAPAROSCOPIC PARTIAL NEPHRECTOMY

a) Introduction

Over the last decade, laparoscopic partial nephrectomy (LPN) has gained acceptance as an alternative to the open procedure. Given its more recent development most LPN series understandably have shorter follow-up compared to most OPN series. The preferred choice of access for LPN is the transperitoneal approach. Retroperitoneal access is reserved for posterior and particularly posteromedial tumours [87]. In the largest LPN series to date, Gill et al reported LPN in 1000 patients over a period of 9 years. Of these, 800 LPNs performed by a single surgeon were stratified according to consecutive time periods (era I (1999-2003), era II (2004-2006) and era III (2007-2008).

Tumours in the most recent era were larger, more commonly ≥ 4 cm, central and hilar, and less often peripheral < 4 cm. Despite increasing tumour complexity, warm ischemia times were shorter, complication rates (overall, post-operative, urologic) were significantly lower, positive surgical margin rate was only 0.6%, and renal functional outcomes were superior in the most recent era. In patients with pathologically-confirmed cancer, 5-year overall, cancer-specific, and recurrence-free survival was 90%, 99%, and 97%, respectively [88].

If a LPN encounters difficulties, the committee recommends that the optimal surgical plan would be to convert to OPN with LRN being performed in the rare case.

b) Indications

The initial experience with LPN was limited to small (< 4 cm), low stage, single, peripheral and exophytic lesions. These indications have also been expanded to include more challenging masses: central tumours, hilar tumours, cystic tumours, multiple ipsilateral tumours, tumour in a solitary kidney, larger tumours (T1b and T2 or greater), and intraparenchymal tumours [89]. With regard to the tumour location, during a surgeon's initial LPN experience, exophytic tumours and non-central tumours not extending into the renal sinus may be excised more easily, with a lower incidence of complications [90] (Fig. 13a – f). A new anatomical classification has been recently proposed to categorize different locations of renal tumours that could correlate with surgical ease and oncological safety of the PN [45]. A comprehensive standardized system for quantitating renal tumour size, location and depth is the recently developed R.E.N.A.L. nephrometry score [46].

LPN for central and hilar tumours

In the past, central location of the tumour or contact of the tumour with a major renal vessel (hilar tumour) on preoperative cross-sectional imaging was considered to be a contraindication for LPN. The reason was the perceived difficulty in achieving negative surgical margins, while preserving adequate blood supply to the renal remnant. However, a prospective study demonstrated that the thickness of the surgical margins has no effect on the risk of local recurrence and a good prognosis can be expected as long as the definitive margins are free of cancer [91]. Data on LPN for centrally located and hilar tumours are limited and definitions on central and hilar tumour are not uniform making comparison of results among different studies difficult.

Venkatesh and co-workers reported that complications of LPN for 123 renal tumours were associated with location of the tumour in the kidney with lower complication rates for exophytic (10%) than for endophytic (47%) and hilar tumours (50%) [92].

Two studies performed in centres with adequate laparoscopic expertise reported that LPN in central tumours was associated with comparable outcome as LPN in peripheral tumours. However, long-term follow-up is needed and a longer ischemia time may ensue for central/hilar tumours [12,93]. Frank et al compared LPN for central (n=154) and peripheral (n=209) tumours. Although the blood loss was similar (median 150 mL) more early postoperative complications occurred in the central tumour group (6% vs. 2%). In addition, central tumours required longer WIT (median 33.5 vs. 30 minutes, $p < 0.001$) [12]. Nadu et al also compared LPN for central tumours (n=53 including 12 hilar tumours) and peripheral tumours (n=159). Four patients (7.5%) had delayed hemorrhage (arterial pseudoaneurysm)

with late onset hematuria; these 4 patients required angiographic embolization. Only one patient had a urine leak (1.9%) after LPN for central tumours. Mean WIT in the central tumour group was longer than in the peripheral tumour group (37 vs. 28 minutes, $P < 0.05$) but the median WIT was similar (30 vs. 29 minutes, $P > 0.05$) [93]. Two recent smaller studies reported that in experienced hands LPN for hilar tumours is feasible and safe while short-term oncologic results are promising [94,95].

LPN for tumour in solitary kidney

A recent study from Lane et al compared 169 OPN and 30 LPN for stage T1 tumours in a solitary functioning kidney. By 3 months after OPN or LPN, the average loss of postoperative renal function was similar. LPN compared to OPN was associated with a longer WIT (mean difference of 9 minutes; $P < 0.0001$), a 2.54-fold higher risk of postoperative complications ($P < 0.05$) and a higher rate of postoperative dialysis (10 vs. 0.6%, respectively, $P = 0.01$). Of note, the T1 tumours in this study were not sub-divided into cT1a (< 4 cm) and T1b (4-7 cm) sub-categories. Although LPN is technically feasible for a tumour in a solitary kidney, at this time OPN may be considered the preferred treatment approach for these patients who are at high risk for CKD [96]. This was recently confirmed in a study including 84 patients with solitary kidney [1].

c) Oncological outcome

Table 3 presents oncologic outcomes of laparoscopic partial nephrectomy [13,37,97-99]. Oncological outcomes are similar when comparing LPN and OPN for localized RCC. A comparison of LPN and OPN performed in 1800 patients with a single renal tumour (< 7 cm) at major centres with greatest expertise showed a similar oncological outcome (3-year CSS: 99.3 vs. 99.2%, respectively) [28]. Lane and Gill reported intermediate-term outcomes of LPN in 56 patients, with an OS and CSS of 86 and 100%, respectively, at 5 years [13]. A retrospective matched-pair comparison of LPN and OPN in 200 pT1 patients showed a 5-year OS of 96% and 85%, respectively. The 5-year local recurrence-free survival was 97% after LPN and 98% after OPN [100]. Most recently, Lane and Gill compared 7-year outcomes of LPN (n=77) with OPN (n=310) for single clinical stage T1 (≤ 7 cm). Cancer recurred infrequently, and only rarely caused mortality, after either LPN or OPN. At 7 years, metastasis-free survival was 97.5% and 97.3% ($p=0.47$) after LPN and OPN, respectively. On multivariate analysis, predictors of all-cause mortality included advancing age ($p < 0.0001$), co-morbidity ($p < 0.0001$), pre-operative renal dysfunction ($p=0.0001$), but not tumour size ($p=0.6$) or operative approach (LPN vs. OPN, $p=0.06$). The authors concluded that LPN and OPN provide similarly excellent long-term overall

Table 3. Oncologic outcomes of laparoscopic partial nephrectomy

Author	No. of patients	Mean tumour size (cm)	CSS (%)	Positive surgical margins (%)	Local recurrence (%)	Mean follow-up (mo)
Porpiglia et al (97)	34	3.2	100	2.9	0.0	16
Gill et al (98)	430	3.6	100 (3-yr)	0.0	0.0	30
Permpongkosol et al (99)	85	2.4	91.4	2.4	2.4	40
Bollens et al (37)	39	3.2	100	2.6	0.0	15
Lane et al (13)	58	2.9	100 (5-yr)	1.7	1.7	68

CSS: Cancer-specific survival

Reprinted from Van Poppel H. Efficacy and safety of nephron-sparing surgery. *Int. J Urol*, 2010;17(4):314-26.

and cancer-specific survival, with the vast majority (97%) of patients experiencing metastasis-free survival [101].

d) Complications

Porpiglia et al recently reported the incidence of complications in recent LPN series from centres with adequate expertise with a total number of 1062 patients. The overall complication rate was 21.4% (range 9 to 33%). There was a 5.1% rate of hemorrhagic complications (range 1.5 - 10.0%), a 4.2% rate of urine leakage (range 1.4 - 13%) and a 0.7% rate of renal failure (range 0.5 - 2.0) [102].

Turna et al reported a large series focusing on complications after 507 LPNs performed by a single surgeon. Of the 107 complications 49 (46%) were urologic. Of total complications, 22 (20.6%) were grade I, 48 (45%) grade II, 32 (30%) grade III, 5 (4.7%) grade IV and none were grade V. Complications were compared for LPNs performed between 1999 to 2002 and 2003 to 2006. Despite the increase in the number of total and complex procedures, there was a decrease in the rate of overall complications (29.6% vs. 16.9%, $P = 0.001$), urological complications (13.6% vs. 7.7%, $P = 0.03$) and nonurological complications (16% vs. 9.2%, $P = 0.02$). Urine leakage rate decreased from 4.7% to 1.2% ($P = 0.01$), while the postoperative hemorrhage rates did not show statistical difference (5.9% vs. 5.6%), likely due to the increased number of complex procedures [44]. Recently, a detailed single-centre review was reported of 144 consecutive LPN (4 surgeons) conducted from November 2002 to January 2008. Standardized grading criteria were used which allows comparison to the series of Turna et al. A total of 39 complications occurred in 29 (20%) patients. Of these, 20 (51%) were urologic. Of total complications 6 (15.4%) were grade I, 19 (48.7%) grade II, 11 (28.2%) grade III and 3 (7.7%) grade IV and none were grade V. Overall results appear consistent with those of other contemporary series of LPN or OPN. Increased American Society of Anesthesiologists (ASA) score and ischemic time are associated with complication risk. Hospital readmission and reintervention was required in 15 (10.4%) and 9 (6.2%) patients, respectively [103].

With the use of more sophisticated laparoscopic techniques and the increased experience of laparoscopic surgeons the complication rate of LPN has significantly decreased and now appears similar to that of OPN [34,44,104].

e) Comparison between LPN and OPN

Gill et al's recent combined study from 3 major centres with greatest expertise compared 1800 patients with a single tumour (< 7 cm) undergoing either LPN or OPN. Advantages of LPN were less operative time, decreased operative blood loss and shorter hospital stay. On the other hand, LPN was associated with a 10 minute longer WIT (31 vs. 20 min) and more postoperative complications (18.6 vs. 13.7%) than OPN, particularly postoperative hemorrhage (4.2 vs. 1.6%) and urologic complications (9.2 vs. 5.0%). Importantly, LPN and OPN were similar with regard to intra-operative complications (1.8% vs. 1%). Shorter operative times and less blood loss with LPN than with OPN, but higher rates of urological complications parallel the findings of a recent meta-analysis of the American Urological Association (AUA) [105]. Oncological outcomes (CSS: 99.3 vs. 99.2% at 3 years), renal function outcomes (97.9 vs. 99.6% at 3 months) and positive surgical margins (1.6 vs. 1%) were similar between LPN and OPN. Local (1.4 vs. 1.5%) and distant (0.9 vs. 2.1%) recurrences were also equivalent. Conversion to open surgery occurred in 2.1% of LPN cases [28].

A retrospective matched-pair comparison of LPN and OPN was recently performed in 200 patients with pT1 RCC. The authors concluded that in experienced hands LPN provides similar oncologic and functional outcomes compared to OPN at a mean follow-up of 3.6 years. Decrease in GFR at last follow-up, positive surgical margin rates, blood loss, and complication rates were comparable for both groups. Operative time, ischemia time and hospitalization time were shorter in the LPN group and conversion rate to open surgery was 2% [100]. How often a conversion to LRN was done is not reported. In addition, studies show that LPN has protective effects on the long-term renal function when compared with LRN [106,107].



Fig. 13a: MRI showing a large angiomyolipoma of the left kidney.

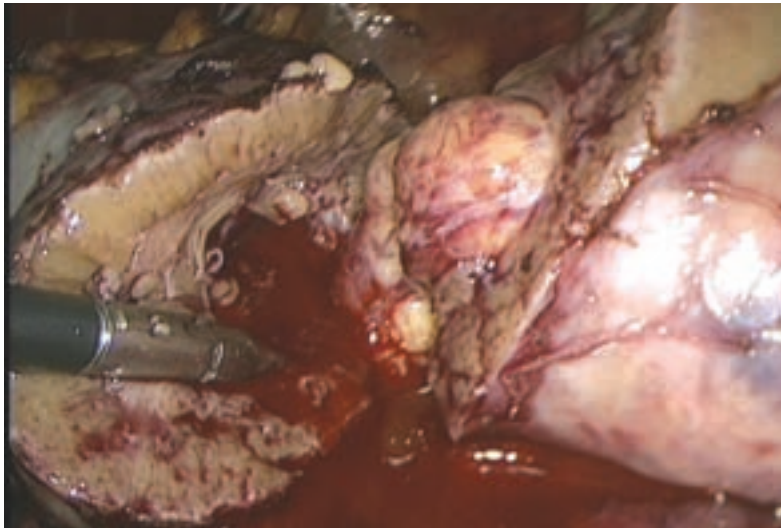


Fig. 13b: The left lower pole is being removed in warm ischemia using cold scissors. The central part of the angiomyolipoma can be seen clearly

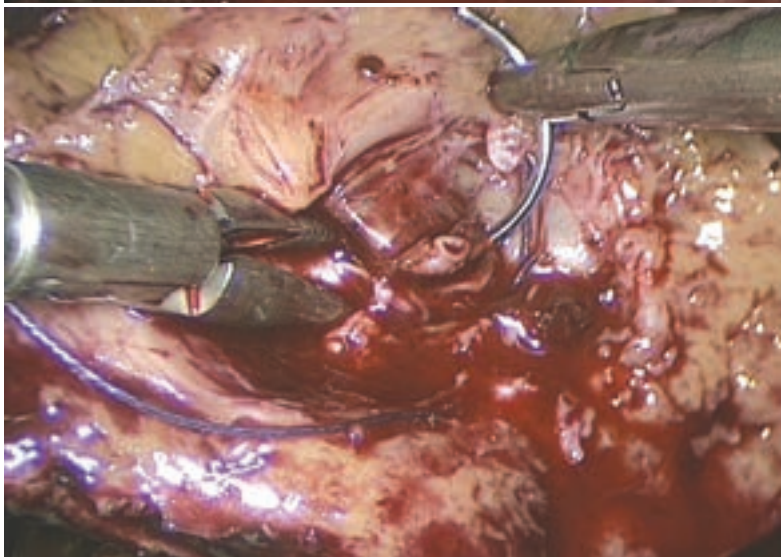


Fig. 13c: The first running suture includes the vessels of the interstitial tissue as well as the collecting system. This suture is secured on both ends with a lapra-ty[®] clip.

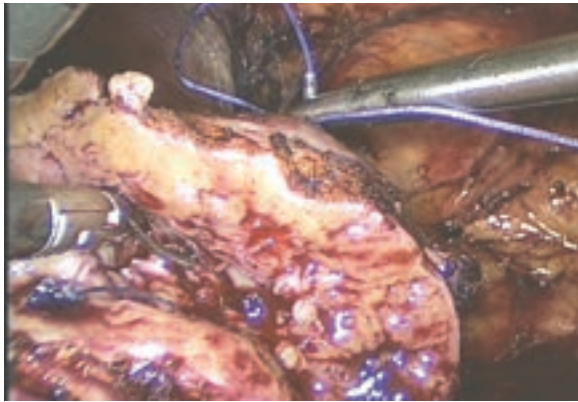


Fig. 13d: A suture through the full thickness of the renal parenchyma helps to approximate the cut edges and provides haemostasis.

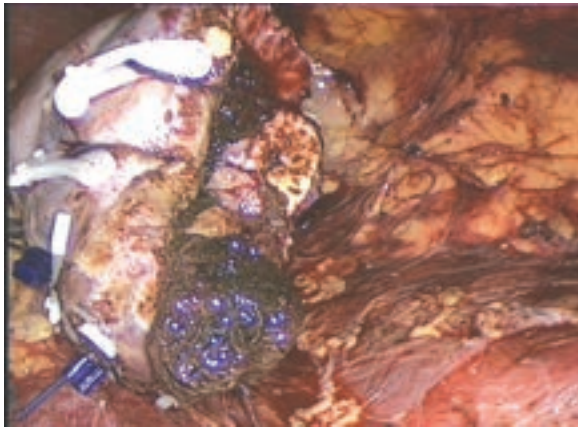


Fig. 13e: The parenchymal suture is secured with large hem-o-lok[®] clips which allow to apply pressure on the renal parenchyma thereby providing optimal haemostasis. A roll of tabotamp[®] is placed underneath this suture to improve haemostasis.

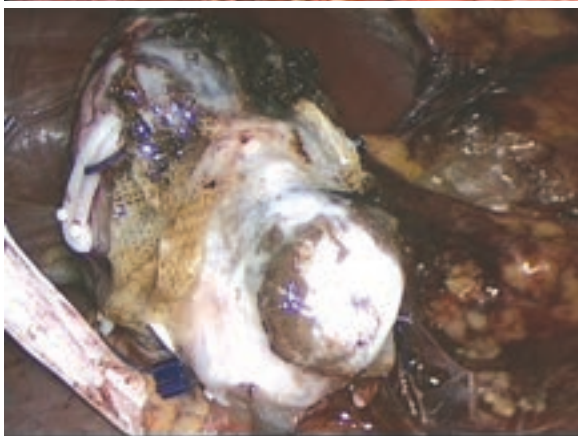


Fig. 13f: Finally, as preventive measure to avoid delayed hemorrhage, the repair is covered with fibrin blue and a strip of tabotamp[®].



Fig. 13g: The excised lower pole with the tumour is placed with an organ bag for safe removal.

f) Contemporary outcomes of LPN: The State-of-the-Art

With increasing LPN experience and standardization of our early unclamping technique, contemporary LPN outcomes have improved significantly. Specifically, the two remaining above-mentioned concerns with LPN have now been addressed, leading to decreased ischemia times and reduced hemorrhage rates.

Gill et al reported a single-surgeon series of 800 LPN cases encompassing a 9-year period (1999–2008) [88]. The authors divided the entire cohort into 3 chronologic eras: Era I: 1999–2003 (n=276), Era II: 2004–2006 (n=289), and Era III: 2007–2008 (n=235). On comparing eras I, II and III, tumours in the most recent era were larger, more commonly ≥ 4 cm, central and hilar, and less often peripheral and < 4 cm (p-value significant for all). Despite such increasing tumour complexity, mean warm ischemia times were shorter in the most recent era: 32 min, 32 min and 14 min ($p<0.0001$). Overall, post-operative and urologic complications were significantly lower in the most recent era. In the most recent era, positive surgical margin rate, and incidence of conversion to OPN or RN were 0.6%, 0% and 2.1%, respectively. Renal functional outcomes were superior in era III, as reflected by lesser percent decrease in estimated GFR (18%, 20% and 11%, respectively). In patients with pathologically-confirmed malignancy (n=744), 5-year overall, cancer-specific, and recurrence-free survival was 90%, 99%, and 97%, respectively. The authors concluded that over this 9-year experience with 800 consecutive LPNs, tumour characteristics and LPN outcomes had evolved significantly. Despite increasing tumour complexity in contemporary practice, the 3 key outcomes of LPN (ischemia time, complications, and renal function) have improved significantly. As a result, the authors routinely offer LPN for the majority of tumours hitherto reserved for open NSS [88].

A recent study from Kavoussi's group compared 'off-clamp' LPN with traditional 'on-clamp' LPN. Significant differences ($p < 0.05$) in the 'off-clamp' group relative to the 'on-clamp' group included shorter operative time (132 vs. 146 min), a higher proportion of exophytic lesions (51% vs. 28%), smaller tumour volume (26 vs. 41 cm³) and less hilar tumours (15% vs. 29%). Short term elevation in serum creatinine was significantly less (6% vs. 29%) although long term significance of this finding is unknown. There were no significant differences in blood loss, transfusion rate, or complications. As experience improves, an increasing number of LPNs may be performed 'off-clamp'.

Finally, Kamoi & Gill compared 150 contemporary patients undergoing OPN (2006–2008) with 150 contemporary patients undergoing LPN (2007–2008). Notably, all OPNs were performed by one

experienced open surgeon (Andrew C. Novick, MD), and all LPNs were performed by one experienced laparoscopic surgeon (Inderbir S. Gill, MD). LPN patients had shorter ischemia time (21 versus 13 minutes, $p<0.0001$), with more LPN patients having ischemia time ≤ 20 min (52% vs. 97%). Post-operative complications were fewer in the LPN group (19% vs. 8.7%; $p=0.01$), including hemorrhage (3.3% vs. 2.7%; $p=ns$) and urine leak (7.3% vs. 1.3%; $p=0.02$). Patients undergoing elective PN had similar, and those undergoing imperative PN or PN in solitary kidney had superior renal functional outcomes in the LPN cohort, likely a result of the reduced ischemia time during LPN. Of note, OPN patients had somewhat larger tumours, more solitary kidneys, and a higher incidence of baseline renal dysfunction; however, after adjusting for each of these baseline demographic differences, LPN outcomes were, at a minimum, equivalent to OPN outcomes in each parameter evaluated.

These emerging new data indicate that, in experienced hands, LPN is now similar to OPN as regards the key outcomes of ischemia time, urologic complications and renal functional outcomes. This improvement in LPN outcomes has occurred despite increasing tumour complexity. As a result, several centres now routinely offer LPN for the majority of technically challenging small tumours such as hilar, central completely intra-renal, larger (4–7 cm, pT1b) tumours or tumours located in a solitary kidney [89].

A recent single-centre study by Lifshitz et al compared the technique and outcome between the early (group 1: 50) and recent (group 2: 50) LPN experience between October 2002 and August 2008. Group 2 had larger tumours (3 cm vs. 2.4 cm, $P=0.002$) and significantly more central tumours (52% vs. 12%, $P=0.001$). In group 2 the authors stopped the use of ureteral catheters and bolster renorrhaphy, and routinely clamped the renal hilum. The WIT (30 and 27 minutes, respectively, $P=0.3$) and complication rates were similar in group 1 and 2. Overall, patients with tumours sized > 4 cm had more complications ($P=0.042$). In group 2, the estimated blood loss (243 vs. 140 ml, $P=0.01$) and hospital stay (2.5 vs. 1.4 days, $P < 0.001$) decreased and the readmission rate was only 5.4%. With growing experience and technical modifications LPN is now performed for patients with larger and more central tumours [108].

5. ROBOTIC PARTIAL NEPHRECTOMY

Shapiro et al reported excellent oncologic outcomes in their recent review of initial experience with robotic PN (n=211). Estimated blood loss, postoperative renal function, surgery time and hospital stay seemed to be equivalent to LPN. Mean WIT ranged from 21 to 32 minutes. Hilar clamping continues to be a difficult aspect of the procedure [109]. Rogers et al reported that robotic PN is safe and feasible in 14 select patients with complex renal tumours including

hilar, endophytic, and multiple tumours [110]. They also evaluated 11 patients from 2 institutions who underwent robotic PN for renal hilar tumours [111]. A recent single-surgeon analysis of consecutive robotic PN (n=40) and LPN (n=62) procedures revealed that robotic PN can produce results comparable to LPN. In the specific author's hands mean WIT (19 vs. 25 minutes, $P = 0.03$), total operative time (140 vs. 156 minutes, $P = 0.04$), and length of hospital stay (2.5 vs. 2.9 days, $P = 0.03$) were shorter for robotic PN than for LPN [112]. The sliding-clip renorrhaphy, a technique adopted by most high-volume surgeons, and the learning curve are both responsible for a significant reduction in overall operative time and WIT [113]. Recently, Ho et al reported 1 year outcomes in 20 patients undergoing robotic-assisted LPN for tumours < 7 cm. There were no late surgical complications, no local recurrence or impairment of renal function [114]. Benway et al reported the largest comparison of robotic partial nephrectomy (n=129) to LPN (n=118) to date, with oncological outcomes and morbidity equivalent to those of LPN. This study combines data from several smaller series that have been updated. Robotic PN appears to offer the advantages of a significant reduction in intraoperative blood loss (155 vs. 196 ml, $P = 0.03$), WIT (19.7 vs. 28.4 min, $P < 0.0001$) and hospital stay (2.4 vs. 2.7 days, $P < 0.0001$) [115]. Very recently, Scoll et al reported the pathologic, perioperative, and renal functional outcomes from the first 100 robot-assisted partial nephrectomy (RAPN) operations performed at their institution during a 21-month period. They included an objective renal mass scoring system (nephrometry) to grade anatomical complexity of the renal tumours resected. Nephrectomy scores of resected lesions were low in 47.9% of patients, medium in 45.7%, and high in 6.4% of patients. Forty-seven percent of patients had tumours > 50% intraparenchymal, and 61.7% had tumours located less than 7 mm away from the renal sinus or collecting system. In 17% of patients, the tumours were touching a first-order vessel in the renal hilum. Mean WIT was 25.5 minutes. Mean change in postoperative GFR improved 6.32 mL/min/1.73 m². Histology was RCC in 81% of tumours. Positive margin rate was 5.7%. Major and minor complication rates were 6% and 5%, respectively. There were 2 conversions to open surgery. RAPN seems to be a safe and technically feasible minimally invasive approach to NSS even in more complex cases, with acceptable pathologic and renal function outcomes comparable to open and laparoscopic PN [116].

Although long-term outcome data are currently lacking, early results with robotic PN demonstrate that it is clinically comparable to LPN. Large prospective, randomised studies are needed to validate preliminary results of robotic PN and compare with current methods.

6. FOLLOW-UP AFTER PARTIAL NEPHRECTOMY

There is currently no consensus on follow-up strategies after surgical extirpation for patients with RCC. Recently, Kassouf et al published the Canadian guidelines for surveillance after nephrectomy for nonmetastatic RCC, based on pathological stage [117]. Grades of recommendations were given using the modified Oxford Centre for Evidence-based Medicine scheme. Patients undergoing PN for pT1 tumours can be followed according to the same surveillance protocol as those undergoing RN since the local recurrence rates in this population are similar to RN (Grade B). Recommended surveillance will include medical history and physical examination, blood screen, and chest X-ray every year. Abdominal CT will be recommended at 24 and 60 months (Grade C). For patients treated with PN, abdominal CT at 3 months to evaluate the residual renal appearance and annual abdominal ultrasound are optional (Grade D) [117].

A recently presented subtype-specific multifactorial protocol can be used to efficiently adapt postoperative imaging to the individual patient [118].

7. CONCLUSIONS

In patients with a clinical T1 renal tumour, PN provides equivalent local tumour control as RN, while minimizing development of new-onset CKD or worsening of existing CKD (Grade B). As such, PN is the established treatment for T1a tumours (< 4 cm) and an emerging standard treatment for T1b tumours (4 to 7 cm) provided that the operation is technically feasible and the tumour can be entirely and adequately removed (Grade B). Any tumour-free surgical margin following PN appears sufficient to prevent local recurrence and disease progression from RCC (Grade B).

In balancing the therapeutic decision between PN and RN, the individual patient's performance status, comorbidities and renal function should be carefully weighed.

Over the years, OPN has been the reference standard nephron-sparing procedure. Today, at centres lacking advanced laparoscopic expertise, OPN remains the first nephron-sparing treatment option. However, at centres with the requisite minimally invasive expertise, LPN is now a routine procedure, with similar peri-operative and long-term outcomes as OPN, albeit with significantly decreased patient complication profile. As such, current indications for LPN have been expanded to include most renal tumours hitherto reserved for open surgery. Larger LPN series with longer follow-up, possibly in a prospective randomised fashion, are necessary. Robotic techniques may increase penetration of minimally invasive PN into the community.

Future research should focus on decreasing the

technical complexity of LPN and finding newer techniques of eliminating or reducing ischemia. In the ultimate analysis, saving nephrons is the more important goal, which supersedes its technical approach, open or laparoscopic. Non-availability of minimally invasive expertise must prompt open partial, not laparoscopic radical nephrectomy.

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VI. ENERGY ABLATIVE THERAPIES FOR LOCALIZED RCC

1. THERMAL ABLATIVE THERAPIES

a) Introduction

Ablation of renal tumours is emerging as a viable minimally invasive alternative to resection for local control of carefully selected tumours. Potential advantages of ablative procedures are reduced morbidity, shorter hospitalization, faster convalescence, preservation of renal function, lower costs and the ability to treat patients who are at high-risk for surgery [1]. On the other hand, patients should accept the need for long-term radiographic surveillance after treatment and should be clearly informed about the non-validated treatment efficacy of ablative therapies [2]. Established ablative modalities include cryoablation and radiofrequency ablation (RFA), both of which can be performed open, laparoscopically, or percutaneously. The laparoscopic approach is preferred in anterior tumours and when mobilization away from the adjacent organs is required to avoid damage. The percutaneous approach is typically reserved for posterior tumours and for patients at increased risk for surgery or anesthesia [3]. All published series using ablative techniques are retrospective observational studies. Despite several concerns, results of thermal ablative procedures in small renal tumours are encouraging. For anatomically uncomplicated small renal masses conventional surgery has shifted to less invasive ablative modalities at some institutions. More complex renal tumours are still treated by PN when technically feasible [4]. Careful patient selection and patient counseling are of paramount importance in the complex decision-making process for the management of renal tumours. Biopsies prior to therapy are strongly encouraged [5].

b) Indications

Ablative therapy is indicated for the management of small, incidentally found renal cortical lesions in elderly patients, patients with genetic predisposition to multiple tumours, patients with a solitary kidney, or bilateral tumours [6]. However, as more experience is gained, it may be extended to the SRM in younger patients and those with a normal contralateral kidney, a similar evolution seen with partial nephrectomy. It has to be noted that at this time, there is no literature to support this. Contraindications include a limited life expectancy of < 1 year or difficulty for successful outcome due to size or location of the tumour. In general, tumours > 4 cm or tumours in the hilum, close to the proximal ureter or central collecting system are not typically recommended for ablation. Absolute contraindications are irreversible coagulopathies or severe medical instability, such as sepsis [6].

Thermal ablation may be best suited for high surgical risk candidates with multiple comorbidities who have small, exophytic renal tumours [7,8]. Nevertheless, it is possible that patients at high risk for surgery who undergo thermal ablation suffer complications that might necessitate surgery. There is no consensus on the maximum tumour size for ablation. Some authors find 3 cm appropriate as maximum tumour size for cryoablation [9] and RFA [10], others suggest a limitation of 3.5 cm [7] or 4 cm [8] above which success rates substantially fall.

c) Concerns with the use of thermal ablative therapies

A primary concern in relation to thermal ablative therapies is the higher local recurrence rate with cryoablation and RFA when compared to surgical excision in recent meta-analyses (4.6%, 7.9%, 2.7 % and relative rates of 7.45, 18.23, and 1.0, respectively) [11,12]. A second concern is the controversy over the validity of the radiographic definition of postablative success. Recent data showed that 46.2% patients (6 of 13 patients) that showed no enhancement on radiographic imaging after RFA demonstrated viable tumour cells at a 6-month post-ablation biopsy [13]. Another weakness is the absence of histopathological confirmation of complete tumour destruction and negative surgical margins [7]. Finally, ablative procedures may preclude or complicate subsequent surgical salvage due to perinephric fibrosis [7]. Long-term oncologic efficacy of ablative procedures remains to be demonstrated. These concerns underscore the need for meticulous selection of patients who today may be potential candidates for thermal ablation.

2. CRYOABLATION

a) Introduction

Cryoablation causes tumour destruction by rapid freeze and thaw cycles. A recent meta-analysis included 496 localized renal tumours that were treated with cryoablation. Mean weighted follow-up after cryoablation was 18.3 months with the procedure selectively performed in older patients with smaller tumours (mean weighted age 65.7 years and mean weighted tumour size 2.56 cm) [12]. One purported advantage of cryoablation over RFA is the ability to perform continuous intraoperative ultrasound monitoring of the ice ball although surgeons experienced with RFA rely on thermal measures at the periphery with similar results. A recent survey of Bandi et al to determine the current practice patterns in the use of ablative modalities for the management of small renal masses at 112 academic centres in the United States revealed that cryoablation (79%) was more frequently used than RFA (55%) [14] (Fig. 13, 14,15).

b) Choice of surgical access – recent findings

At present, > 75% of the reported renal cryoablation treatments has been applied through an open or laparoscopic approach. Percutaneous image-guided techniques have been used much less frequently [15]. Recently, Finley et al retrospectively reviewed 18 patients (19 tumours) who underwent percutaneous cryoablation and 19 patients (24 tumours) who had laparoscopic cryoablation. Percutaneous cryoablation was associated with a statistically significant decrease in operative time, hospital stay and narcotic use and a trend towards fewer complications. The overall complication rate was lower after percutaneous cryoablation (22.2% vs. 40%). The authors considered percutaneous cryo ablation the treatment of choice for posterior, lateral and select anterior renal lesions of 3 cm or smaller [16]. Bandi et al conducted a telephone survey to evaluate analgesic requirements, complication and patient satisfaction after probe ablative procedures. They also found faster complication for the percutaneous approach, but did not find a difference in the median opioid analgesic requirement, and patient satisfaction [17]. In a recent comparative study, percutaneous renal cryo ablation has been deemed safe and effective and associated with lower hospital charges than laparoscopic cryoablation [18]. Recently, single-port laparoscopic and natural orifice transluminal endoscopic surgery approaches have also been used for renal cryo ablation [19,20]. Very recently, a prospective pilot study showed that stereotactic percutaneous cryoablation for renal tumours offers the potential for safe, precise cryo probe placement [21].

c) Oncological outcome

Current 3-year laparoscopic cryoablation data offer

CSS rates of 98% [22,23] and 100% [24] and an OS of 89% [22]. Davol et al reported a 5-year CSS rate of 100%. The cancer-free survival rate after a single cryoablation procedure was 87.5% and improved to 97.5% after a repeat procedure [25]. Mean renal tumour size in these studies was less than 2.7 cm. Three and 5-year survival data are promising and indicate that renal cryo ablation could be a good alternative in appropriately selected patients who are considered unsuitable for PN or active surveillance. In a recent single-centre study laparoscopic renal cryoablation (n=52) and percutaneous renal cryoablation (n=20) achieved good cancer control with minimal morbidity at a mean follow-up of 30 months in a patient cohort with numerous comorbid conditions. Percutaneous renal cryo ablation had a significantly higher primary treatment failure rate [5] than laparoscopic renal cryoablation [2], but retreatment offered salvage cancer control with no significant complications. Overall CSS and cancer-free survival were 100% and 97%, respectively [26].

Table 4 presents the oncologic outcome in selected studies of cryoablation [22,23,25,27-30]. Very recently, Aron et al presented long-term oncological outcomes in patients treated with laparoscopic renal cryoablation by a single surgeon. They report on 80 patients with a minimum 5-year follow-up after cryoablation for a small renal mass, including 92% 5-year disease specific survival and 84% overall survival in the 55 patients with biopsy proven RCC. Of these 55 patients 11 (14%) had recurrence, including local recurrence in 5, locoregional recurrence with metastasis in 2 and distant metastasis without locoregional recurrence in 4. Median follow-up was 93 months (range 60 to 132). Mean tumour size was 2.3 cm (range 0.9 to 5.0 cm), median ASA score was 3 and mean BMI was 28 kg/m². A disease specific survival rate of 83% at 10 years is possible. The authors recommend cryoablation as the initial

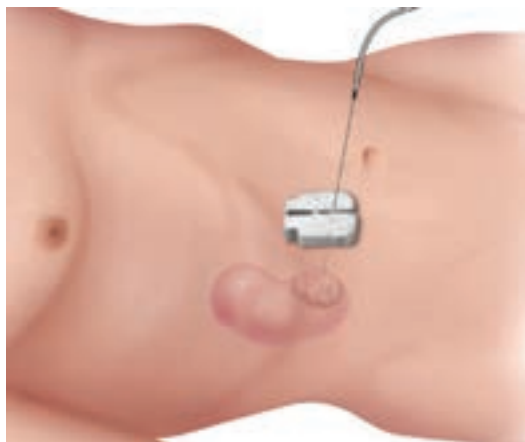


Fig. 14: Drawing of a cryoneedle being inserted transcutaneously into a right lower pole anterior renal tumor. A template can be placed on the skin to be used as a trajectory guide.



Fig. 15: Drawing of a transabdominal laparoscopic view of a cryoneedle being percutaneously inserted into an exophytic, polar tumor. One or several needles can be placed to provide sufficient ice to achieve cellular kill of the tumor along with a surrounding margin of parenchyma.

treatment in patients with a small renal mass who are not suitable candidates for PN [31].

d) Impact on renal function

In a recent retrospective analysis of 123 patients, laparoscopic renal cryoablation appears to have minimal impact on renal function, as measured by serum creatinine and creatinine clearance levels. It can be performed regardless of the preoperative renal function [32]. The recent study by Aron et al also shows that cryoablation has minimal impact on renal function. The eGFR before vs. after treatment was 66 vs. 59 ml per minute per 1.73 m² [31].

e) Complications

A multi-institutional review by Johnson et al demonstrated that cryoablation has a low complication profile when used to treat small renal tumours (13.7%; minor 12.2%, major 1.4%) [33]. The most common complication was pain or paraesthesia at the probe insertion site (7.2%).

Recently, it has been shown that laparoscopic cryoablation of larger renal masses (≥ 3 cm) may be associated with increased morbidity and therefore should be reserved for tumours with diameter < 3 cm [9]. On the other hand, in another recent study, percutaneous cryoablation of anteriorly located tumours and tumours > 4 cm in diameter was found technically feasible and relatively safe when performed in an experienced centre [34]. Limitations of these studies were the retrospective design and

the short follow-up.

More recently, Laguna et al prospectively collected multi-institutional data on laparoscopic renal cryoablation with ultrathin probes in 144 patients. Perioperative negative outcomes including conversion occurred in 17% of cases. Complications according to the Clavien system occurred in 15.5% of the cases; however most of the complications were Clavien grade 1 or 2. Increasing tumour size, the presence of cardiac conditions and female gender were associated with a higher risk of developing a complication. The authors confirmed the tumour size cut-off of 3.4 cm as an adequate predictor of negative outcomes. This study confirms the relative safety of laparoscopic cryoablation [35].

f) Multiple renal tumours

A recent study shows that synchronous cryoablation is relatively safe and feasible for patients with multiple ipsilateral renal lesions that could be very challenging to address with an extirpative approach. Five patients had ablation of 2 renal lesions, 1 had 3 lesions, and 1 had 4 lesions. The mean greatest diameter of any single tumour was 2.0 cm (range 0.7 – 7.5 cm). Cryoablation of the 17 lesions was associated with few complications and with a median follow-up of 23.3 months (range 7-28 months), serum creatinine in most patients had not significantly changed. No tumour recurrences have been detected on postoperative imaging [36].

Table 4 : Selected studies of cryoablation

Study	Approach	No. tumours	Median tumour size (cm)	Follow-up (mo)	CSS (%)	Tumour recurrence after one ablation (%)
Gill et al (22)	lap	56 (36 proven RCCs)	2.3	36 (mean)	98	3.6
Schwartz et al (27)	lap/open	85 (50 proven RCCs)	2.6	10 (mean)	—	2.4
Davol et al (25)	lap/open	48 (38 proven RCCs)	2.6	64 (median)	100	12.5, 2.5
Hegarty et al (23)	lap	179 (No. of RCC not given)	2.5	36 (median)	98	1.7
Cestari et al (28)	lap	37 (29 proven RCCs)	2.6 (mean)	20.5 (mean)	—	5.7
Silverman et al (29)	PC	26 (24 proven RCCs)	2.6	14 (mean)	—	13
Aron et al (30)	lap	88 (No. of RCC not given)	2.3	83 (median) (range: 60-120)	95: at 5-yr	22: at 5 years

PC: percutaneous; lap: laparoscopic; CSS: cancer-specific survival; RCC: renal cell carcinoma

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g) Increased risk of relapse after cryoablation – which lesions fail?

A recent study analyzed 163 patients who underwent laparoscopic cryoablation (LCA) between 2001 and 2008 with at least 6 months of follow-up. Median tumour size was 2.4 cm (range 0.5-5.0). LCA showed good tumour control over a 5-year follow-up, with an acceptable recurrence rate. For each 1 cm increase in tumour size there was a 4-fold increase in the probability of local recurrence. Endophytic tumours (in 22.8% patients) were 11 times more likely to recur in this series. Larger tumours and those with endophytic growth pattern may be at increased risk of relapse after LCA [37].

Another recent study analyzed 47 renal lesions that underwent LCA. Median tumour size was 2.7 cm (range 1.2-5.4) and median follow-up was 13 months. Treatment failure was noted in 8 of 47 lesions (17%), 7 of which (87.5% of failed lesions) had broad-based contact with the renal sinus. Lesions with broad-based contact with the renal sinus were successfully treated in 53.3% of the time whereas lesions not in contact with the renal sinus were successfully treated in 96.9% ($P < 0.01$) of the time. The authors suggest that renal lesions which make broad-based contact with the renal sinus are at a significantly higher risk of failure of LCA [38].

3. RADIOFREQUENCY ABLATION

a) Introduction

RFA causes tumour coagulation by converting the radiofrequency waves to heat, resulting in thermal tissue damage [1]. RFA is one of the most recently developed treatment modalities for localized RCC and a standard technique is still lacking in the current literature. A recent meta-analysis included 607 localized renal tumours that were treated with RFA. Mean weighted follow-up after RFA was 16.4 months. RFA was selectively performed in older patients with smaller tumours (mean weighted age 67.2 years and mean weighted tumour size 2.69 cm) and is considered a viable treatment option [12]. Patient demographics and selection criteria for RFA are similar as for cryoablation treatment, mainly for older and high surgical risk patients and tumours with diameter < 3 cm. Gervais et al treated 100 tumours in 85 patients by percutaneous RFA and showed that small-sized tumours (< 3 cm) and exophytic tumours were predictive factors for complete coagulation [10]. A study including 16 patients (20 tumours) with a minimum of 4 years follow-up revealed that RFA treatment of exophytic RCC (< 5 cm) is effective in destroying the tumour and comparable to surgical excision at 4 years [39]. A meta-analysis by Kunk and Uzzo demonstrated that patients treated with RFA may require re-ablation more frequently than those treated with cryoablation (8.5% vs. 1.3%, respectively) [15]. Compared with cryoablation, a

large proportion of tumours managed with RFA had unknown or indeterminate pathology (42.8% vs. 17.7%) [12] which could lead to an overestimation of the actuarial specific CSS rates for RCC. Both phenomena may be attributable to the fact that the majority of RFA cases are performed percutaneously. Biopsy is not consistently performed and re-ablation rates are significantly higher when a percutaneous approach is used. Re-ablation rates seem to correlate with surgeon specialty (interventional radiologist or urologist) [40]. Difficulty of reoperation after ablation also depends on the location of the prior ablation.

b) Choice of surgical access – navigational tools and real-time monitoring systems for RFA

RFA can be performed percutaneously or laparoscopically under ultrasound, CT- or MRI-guidance. Currently, about 94% of the reported renal RFA treatments have been performed through the percutaneous approach [15], mostly under CT-scan guidance [41]. Only a few centres have used the laparoscopic approach for RFA ablation. To date, no randomised controlled trials have been conducted to compare laparoscopic and percutaneous RFA or to compare RFA and cryoablation. Data in the literature revealed that although the percutaneous approach is less invasive, RFA and cryoablation re-ablation rates are significantly higher when a percutaneous approach is used and seemed to correlate with surgeon specialty (interventional radiologist or urologist) [40]. Recently, sophisticated navigational tools and real-time monitoring systems for RFA are being investigated. Carey and Leveillee reported the use of non-conducting temperature probes, independent of the RFA electrode, in order to achieve real-time temperature monitoring of the ablation zone. Ablations were continued until the peripheral and deep temperature probes registered 60°C for at least 15 seconds. All 37 renal tumours between 3 and 5 cm in 36 patients could be successfully ablated in one session. There were two radiographic failures at 9 and 30 months that required second treatment (95% radiographic success rate). This technique reduces the need for retreatment sessions, decreases the incidence of retreatment of the normal parenchyma and prevents collateral damage of the adjacent organs [42]. Moreover, a recent study has demonstrated that RFA with peripheral fiberoptic real-time temperature monitoring is able to improve the success rate for endophytic or centrally located renal tumours. In total, 37 of 41 (90.2%) endophytic, hilar, or central tumours were treated successfully in one session [43]. Ukumura et al described the use of real-time virtual ultrasonography (RVS) as a new and promising alternative imaging method for percutaneous RFA of solid RCC. All 10 patients with 13 RCC were treated successfully in one session and none of them had a local tumour recurrence during the follow-up period [44].

c) Oncological outcome

Table 5 presents the oncologic outcome in selected studies of RFA [23,39,45,46]. After laparoscopic or percutaneous RFA with a mean follow-up period of 25 months recurrence-free survival, CSS and OS were 96.8%, 98.5%, and 92.3% (68% were RCC). Mean renal tumour size was 2.4 cm [46]. Long-term data after 34 percutaneous RFA procedures for small renal masses (mean size 2.0 cm) were recently reported. The overall recurrence-free survival was 90.3% at a mean follow-up of 61.6 months and 79.9% for pathologically confirmed RCC at a mean follow-up of 57.4 months [47]. A recent multi-institutional study that used general anesthesia-assisted, contrast-enhanced CT-guided percutaneous RFA to treat 163 masses in 151 patients demonstrated excellent intermediate-term outcomes and a high initial ablation success rate. However, endophytic and interpolar lesions were at higher risk for recurrence. The median follow-up was 18 months (range, 1.5–70). Overall 1- and 3-year recurrence-free survival was 97% and 92%, respectively [48]. Further studies of large numbers of patients with long-term follow-up are needed.

d) Tumour size and success of RFA treatment

Zagoria et al demonstrated in a large series of percutaneous RFA a significant correlation between the size of the renal mass and success of RFA treatment. They reported that CT-guided percutaneous RFA can accurately destroy RCCs smaller than 3.7 cm. Of the 125 treated and biopsy-proven RCC's in 104 patients, 116 (93%) were completely ablated (109 after one session, 7 of the 16 failures after a second session). RFA achieved complete ablation after one session in all 95 RCCs smaller than 3.7 cm and in only 14/30 RCCs larger than 3.7 cm [45].

e) Impact on renal function

Several authors have sought to better define the renal impact of RFA on renal function. Lucas et al concluded that patients with small renal masses < 4 cm undergoing RN or PN were 34.3 and 10.9 times more likely, respectively, to develop stage 3 CKD compared with those who were treated with RFA [49]. Two studies focused on RFA for solitary kidney. In the small study by Jacobsohn et al creatinine clearance declined by 13.3% one week after ablation and by 9.1% at a mean follow-up of 15.3 months [50]. In the study by Raman et al GFR declined by 7.5%, 6 weeks after ablation and remained stable up to 18 months and later [51]. In a more recent study Raman et al analyzed the outcomes from 89 patients with renal masses in a solitary kidney including 47 RFAs and 42 OPNs at a median follow-up of 18.1 and 30.0 months, respectively ($P = 0.02$). Compared to RFA, patients treated with OPN using cold ischemia had a greater decline in GFR at all times evaluated, including soon after the procedure (15.8% vs. 7.1%), 12 months after surgery (24.5% vs. 10.4%) and at the last follow-up (28.6% vs. 11.4%; all $P < 0.001$). Median age (65.9 vs. 59.6 years, $P = 0.03$) and ASA score (3.0 vs. 2.0, $P = 0.01$) were both higher in patients treated with RFA. The median tumour size (3.9 vs. 2.8 cm, $P = 0.001$) was greater for tumours treated by OPN while the median preoperative GFR was lower in the RFA group (46.5 vs. 55.9 ml/min/1.73 m² for OPN, $P = 0.04$). The authors concluded that RFA might be an attractive option for managing tumours in a solitary kidney at risk of declining function [52]. In a recent retrospective analysis of 63 healthy patients with small renal cortical tumours, RFA appears to have minimal impact on renal function, as measured by changes in GFR. The median GFR before and after ablation was 76.3 and 74.3 mL/min/m² [53].

Table 5 : Selected studies of RFA

	Approach	No. tumours	Median tumour size (cm)	Follow-up (mo)	CSS (%)	Tumour recurrence after one ablation (%)
Zagoria et al (45)	PC	125 (125 RCCs)	2.7	13.8 (mean)	98	13*
McDougal et al (39)	PC	20 (all RCCs)	3.2	55.2 (median)	94	5
Hegarty et al (23)	PC	82 (No. of RCC not given)	2.5	12 (median)	100	11.1
Park et al (46)	PC/lap	94 (65 RCCs)	2.4 (mean)	25 (mean)	98.5	3.2

CSS: cancer-specific survival; RCC: renal cell carcinoma; PC: percutaneous; lap: laparoscopic. * All tumours recurring were > 3.7 cm.

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f) Complications

A multi-institutional review of Johnson et al demonstrated that RFA has a low complication profile when used to treat small renal tumours (8.3%; minor 6.0%, major 2.2%) [33]. The most common complication was pain or paraesthesia at the probe insertion site (3.0%). Two recent RFA studies failed to find a significant association between tumour size and likelihood of complications [45,54]. Veltri et al found that exophytic growth of the tumour is associated with a decreased risk of complications ($P < 0.0380$) [54]. Weizer et al recommend restricting percutaneous RFA to exophytic, posterior and polar lesions or tumours < 3 cm in diameter. Their experience with percutaneous RFA in 24 patients including 32 tumours revealed that thermal complications might be more likely with anteriorly or centrally located tumours, multiple tumours treated in the same setting and in patients with prior PN [55]. In a recent review paper Park et al discuss the most common major and minor complications resulting from image-guided RFA of RCC with an emphasis on causes, possible prevention strategies and imaging features. Similar to cryotherapy, major complications include bowel injury, ureteral injury, massive bleeding and residual or recurrent tumour. Minor complications include pain, hematoma, hematuria, neuromuscular injury, pneumothorax, infarction and inflammatory tract mass. The most common cause of complications is the close proximity of the tumour to neighbouring organs (bowel, ureter). Non-invasive methods to prevent these ablation-related complications include changing the patient's position and using the RF electrode as a lever [56]. Invasive methods to avoid bowel injury involve instillation of fluid or CO_2 between the tumour and the bowel [57-59]. After introduction of a 20- to 22-gauge fine needle under imaging guidance, dextrose in water is instilled into the space between the tumour and the adjacent bowel to increase the distance between the organs and reduce thermal conduction [57]. Dextrose in water is preferred for hydrodisplacement to normal saline because of its non-ionic and iso-osmolar nature [60]. In addition, collecting system and bowel injuries associated with RFA or cryoablation can be avoided by better patient selection based on the patient and tumour characteristics. Care must be taken to avoid damage to the collecting system that may result in loss of the kidney.

g) Comparison between techniques

There are currently no prospective studies comparing cryoablation to RFA or to other forms of nephron-sparing surgery. Long-term results comparing conventional OPN to cryoablation are expected.

h) Comparison of laparoscopic PN with laparoscopic renal cryoablation

Desai et al reported that compared to cryoablation,

LPN was associated with greater blood loss and significantly higher incidence of delayed complications after hospital discharge. The overall complication rate (intraoperative, postoperative and late complications) was 5-fold higher (32% vs. 6.7%) with LPN compared with cryoablation. Both groups were comparable with regards to operative time, hospital stay, convalescence and postoperative renal function. Local recurrence was detected over a mean follow-up time of 5.8 months (0.6%) after LPN and 24.6 months (3%) after cryoablation [61]. A more recent matched-cohort comparison between LPN and laparoscopic cryoablation in elderly patients showed that LPN had a higher mean estimated blood loss, a longer operative time and higher relative risk of open conversion. However in this small retrospective evaluation of laparoscopic cryoablation and LPN, the overall clinical outcome was similar in terms of morbidity, length of hospital stay and changes in creatinine and hematocrit after surgery. No recurrences were observed in either group, with a similar follow-up of 9.8 and 11.9 months, respectively [62].

Several groups have shown the ultimate 3-year and 5-year CSS after laparoscopic cryoablation to be 98% to 100% [22,24-26,28,63] which is equivalent to the 5-year CSS (100%) after LPN of small clinically localized renal masses presented by Lane and Gill [64].

i) Comparison of cryoablation and RFA

Currently, CSS rates of cryoablation [22,24,25,28] and RFA [39,45,46] are relatively similar (97 - 98%, respectively) [41]. A recent meta-analysis by Kunkle and Uzzo compared the outcome of cryoablation ($n=600$; 65% laparoscopically) and RFA ($n=775$; 94% percutaneously). Cryoablation was associated with a lower re-ablation rate (1.3% vs. 8.5%), lower local tumour progression rate (5.2% vs. 12.9%) and less metastases (1.0% vs. 2.5%, $P = 0.06$) than RFA. Pretreatment biopsy was performed more frequently in the cryoablation group (82.3% vs. 62.2%) [15]. In another meta-analysis by Kunkle et al cryoablation was also associated with lower rates of local recurrence and metastatic progression (4.6% vs. 11.7% and 1.2% vs. 2.3%) compared with RFA [12]. The meta-analyses were flawed in that they consisted of retrospective series each with their own selection biases [65,66]. Furthermore, RFA was primarily performed percutaneously (compared to laparoscopic cryoablation) where incomplete treatment and re-ablation is more commonly acceptable since re-treatment is easier to perform. Hegarty et al found in their retrospective comparative analysis a CSS of 98% after 3-years of follow-up in the laparoscopic cryoablation group ($n=164$) and 100% after 1-year follow-up in the percutaneous RFA group ($n=82$). The rate of radiologic relapse of tumour was 1.8% in the cryoablation group versus 11% in the RFA

group. Overall complication rates were low for both groups [23]. The problem in comparing the efficacy of ablative techniques is that especially studies with percutaneous approach tend to give overall results in terms of CSS without stating the number of repeat procedures needed. Primary efficacy is an important endpoint. In a recent meta-analysis by Hui et al, the primary efficacy rate was 87% after a percutaneous approach and 94% after an open or laparoscopic approach ($p < 0.05$) with a mean follow-up of only 15 ± 8 months. The secondary efficacy (after repeated treatments) in the percutaneous treatment group (92%) was not significantly different from that in the laparoscopic or open treatment group. The percutaneous approach was safer than the surgical approach (complication rate 3% vs. 7%) and was equally effective but more than one procedure was required to treat the tumour completely [67]. In a multi-institutional review, Johnson et al analyzed complications associated with cryoablation and RFA performed laparoscopically or percutaneously. Complication rates for cryoablation and RFA were 13.7%, (minor 12.2%, and major 1.4%) and 8.3% (minor 6%, major 2.2%) respectively. The most common complication was pain or paresthesia at the probe insertion site. Complications can be attributed to the approach as well as to the ablation alone [33]. Several studies have demonstrated minimal impact on renal function following cryoablation [22,32,68] or RFA [49-51,53]. At this time, there is insufficient long-term data available to show efficacy of ablative therapies to make comparisons between the ablative techniques.

j) Comparison between PN and RFA

Stern et al recently reported in a retrospective study that at intermediate follow-up (mean 30 months) RFA (14 laparoscopic/26 percutaneous) for patients with cT1a renal tumours has comparable intermediate oncological outcome to PN (30 open/7 laparoscopic). The 3-year recurrence-free survival rate for all patients was 93.4% and 95.8% for the RFA and PN groups, respectively [69]. However, longer term data are needed.

k) Follow-up after thermal ablative therapies

Because follow-up after ablative therapy lacks histopathological confirmation of tumour destruction, some centres prefer to add post-ablation biopsies to radiographic imaging [22]. Current imaging techniques are limited to monitor recurrences and post-ablation biopsies are encouraged when recurrence or incomplete ablation is suspected or as routine in all cases [13]. Existing follow-up criteria are not well-defined and should be more precise and standardized based on radiological and histological factors. In radiological terms, a successfully ablated lesion shows absence of enhancement after contrast injection and shrinkage within time. A blanco CT or

MRI have to be systematically performed before contrast injection to rule out calcifications secondary to small hemorrhages during the procedure. After cryoablation a CT scan tiny enhancement rim may show up in up to 20% of the cryolesions. This rim progressively disappears during the 9 months following cryoablation [70]. Weight et al tried to determine a correlation between imaging findings and histopathology after probe ablation procedures. They demonstrated a poor correlation between post-RFA radiographic imaging and post-RFA biopsy results and an excellent correlation between the radiographic findings after cryoablation and subsequent percutaneous biopsy of the treated lesions. In this study, 6 of 13 patients (46.2%) that showed no enhancement on radiographic imaging after RFA demonstrated viable tumour cells at a 6-month post-RFA biopsy. The 6-month post-ablation biopsy reduced the success rate of RFA from 85% to 64.8% [13]. Raman et al recently suggested that presence of tumour architecture on early (< 12 months) biopsy following RFA may be unreliable. They showed that no viable tumour was present in lesions that were biopsied more than 1 year following RFA [71]. A multi-institutional study revealed that in most cases initial treatment failure following ablation was detected within the first 3 months. Results support a minimum of 3 to 4 abdominal imaging studies in the first year after ablative therapy at months 1, 3, 6 (optional) and 12 [2]. There is no consensus on the optimal follow-up of thermal ablative therapies. Some experts find that this statement does only pertain to RFA because the re-ablation rate is much higher and does not pertain to cryo ablation. A recent laparoscopic cryo ablation study demonstrated that of the 5 (15.6%) ablation sites that showed enhancement at 3 months three persisted by 6 months, but only one displayed enhancement by 9 months. This patient with persisted enhancement by 9 months underwent PN that demonstrated no recurrent cancer [72]. Currently, computed tomography (CT) and magnetic resonance imaging (MRI) are usually performed to evaluate residual or recurrent disease after RFA and cryo ablation of a renal tumour [73].

4. NOVEL TREATMENT MODALITIES OF RENAL MASSES

Other minimally invasive techniques such as High Intensity Focused Ultrasound (HIFU), Radiosurgery, Microwave Thermotherapy (MWT), Laser Interstitial Thermal Therapy (LITT), and Pulsed Cavitational Ultrasound (PCU) should at this time be considered experimental. Clinical series are small and no long-term follow-up data have been reported.

a) High Intensity Focused Ultrasound

HIFU is attractive as non-invasive therapy of malignancies, because there is no need to puncture

the tumour and therefore no risk of hemorrhage or tumour spillage [74]. However, limited clinical data on extracorporeal HIFU of renal tumours show insufficient results [75-78]. The technique is found to be well tolerated with no serious perioperative complications but the eradication of the tumour is inadequate, mainly due to acoustic complexity of intervening structures and the respiratory movements of the kidney [79]. An additional disadvantage is the inability to monitor treatment progression in real time [79].

Problems with respiratory movements of the kidney and acoustical interphases of the abdominal/thoracic wall and tissue inhomogeneities within the kidney are avoided when the transducer is brought directly to the target by laparoscopic HIFU [74,79]. A phase I study by Klingler et al using laparoscopic HIFU ablated 10 renal tumours less than 3 cm in diameter. No HIFU-specific complications were observed in the study. Laparoscopic HIFU is a novel approach that may achieve a greater rate of tumour destruction but further studies to refine the technique are needed [80]. To date, HIFU has to be considered experimental. Honeck et al, recently showed in an *ex vivo* model of the isolated perfused porcine kidney that magnetic resonance imaging (MRI) is potentially a good diagnostic tool for visualizing and monitoring the effects of HIFU ablation of renal masses. Before this imaging modality can be used under clinical conditions, further technical development is essential, especially with regard to reducing the measuring times [81]. A recent 3-year follow-up study evaluated the safety, feasibility and efficacy of HIFU in 17 patients with radiologically suspicious renal tumours (mean tumour size 2.5 cm). Renal HIFU achieved stable lesions in two-thirds of patients, with minimal morbidity, and might be appropriate in selected cases [82].

b) Radiosurgery (Cyberknife)

The Cyberknife is a frameless image-guided radiosurgery device. The 2 main elements are the radiation produced by a small linear accelerator and a robotic arm that allows the energy to be directed at any part of the body from any direction. The Cyberknife divides the high-dose radiation necessary to ablate the lesion completely into up to 1200 separate radiation beams. The individual dose of each radiation beam induces very little effect on the surrounding tissue. However, high radiation doses are delivered to the focal point, destroying tumour tissue and minimizing collateral damage [83].

Ponsky et al reported a phase I study involving 3 patients with a renal tumour of ≤ 4 cm who underwent radiosurgery followed by a PN after 8 weeks. The patients were treated with a radiation dose of 4 Gy per fraction for 4 fractions. No acute toxicities and no changes in renal function were noted, with a mean

follow-up of 12 months. One patient had a necrotic tumour while two others had pathologic evidence of viable RCC [84]. The results were promising considering that in animal models, ablation was not observed until a target of 40 Gy was obtained [83]. Preclinical data showed that radiosurgery (single doses of 24-40 Gy) for predetermined lesions in 16 porcine kidneys with sequential histological evaluations at 4, 6 and 8 weeks achieved complete fibrosis after 8 weeks [83].

In a prospective study including 30 patients, the safety and local efficacy of radiosurgery in metastatic or inoperable primary RCC was evaluated. In total, 82 lesions were treated with high-dose fraction stereotactic radiotherapy. Dose/fractionation schedules varied depending on target location and size (8 Gy x 4, 10 Gy x 4, 15 Gy x 2 or 14 Gy x 3) [85]. Radiosurgery is a promising new technology as it resulted in a high local control rate with generally low toxicity. However, radiosurgery is currently an experimental modality and the first human studies in patients with localized RCC are underway. At present, the role of radiosurgery for the management of renal tumours is unclear and further studies are needed to address its oncological and functional results.

c) Other modalities

1. MICROWAVE THERMOTHERAPY

In MWT, microwave energy is delivered through an antenna inserted directly into the lesion causing an electromagnetic field, which leads to ion oscillation and increase in kinetic energy which is converted to heat, resulting in coagulative necrosis. MWT may generate heat 100 times faster than RFA and may be less susceptible to the heat sink phenomenon. MWT did not appear to be effective for destruction of experimental VX-2 renal tumours in rabbits [8]. MWT followed by nephrectomy has been evaluated in a single phase I study in which it could safely and quickly generate large ablation lesions of renal neoplasms. No skip areas were observed within the ablation zones [86]. In a recent pilot study of 12 patients with pathologically proven RCC (1.3 to 3.8 cm in diameter) ultrasound guided percutaneous microwave ablation appears to be safe and effective. Complete necrosis was induced in a single session in all tumours. No complications were observed, perhaps in part due to the exclusion of tumours adjacent to the bowel and ureter. No residual tumour or recurrence was observed at a median follow-up of 11 months (range 4 to 20). The ablation zone was well defined on contrast enhanced CT and contrast enhanced ultrasound, and it gradually shrank with time. Additional experience with this technique should be required before its widespread clinical use [87].

2. LASER INTERSTITIAL THERMAL THERAPY

LITT also known as Laser Thermal Ablation (LTA) delivers energy through insertion of laser fibres into the tumour, followed by coagulative necrosis by raising the tissue temperatures to $> 55^{\circ}\text{C}$ [1,88]. In a pilot study of 9 patients unsuitable for surgery, MRI-guided LTA of renal tumours was proven safe, feasible (being well tolerated by the patient) and significantly reduced the mean percentage enhancement (% of approximate tumour volume that is viable) from 73.7% before to 29.5% after ablation. However, the clinical implications of this finding are not clear [89,90].

3. PULSED CAVITATIONAL ULTRASOUND

A limitation of thermal ablation is that the thermal zone of destruction cannot be precisely predicted due to subtle differences in tissue character, tissue heterogeneity and variations in blood perfusion [91]. The transcutaneous, nonthermal, mechanical effects of US waves (cavitation) were thought to have an advantage over temperature-based ablation systems. PCU utilizes cavitation effects to destroy the tumour by varying acoustic parameters. The delivery of transcutaneous high intensity ultrasound to induce cavitation tissue ablation is termed histotripsy. Cavitation is a phenomenon by which alternating zones of compression and rarefaction induce microbubble formation, which leads to subcellular tissue fragmentation [91]. With this approach no thermal collateral damage is caused to adjacent tissues, structures or collecting system. Data about PCU are limited to two preclinical studies involving an *in vivo* porcine model [91] and an *in vivo* study in rabbits [92]. Additional research is needed to optimize the parameters for *in vivo* cavitation tissue ablation, including the impact of tissue perfusion and to elucidate any relationship between metastasis and histotripsy treatment [91].

5. CONCLUSIONS

Cryosurgery and RFA by open, laparoscopic or percutaneous approaches are promising minimally invasive nephron-sparing treatment options for localized RCC for most small (mainly $< 3.0\text{ cm}$), low grade renal tumours in patients who are at high surgical risk. However, no randomised comparisons have been performed between the outcome of ablative techniques and RN or PN. Cryoablation and RFA are associated with acceptable short and intermediate survival results and low morbidity. However, long-term oncological outcome remains to be established. Retrospective, non-controlled studies suggest that cryoablation may be associated with a lower re-ablation rate and local recurrence rate compared with RFA. However, variables as surgical approach (laparoscopic versus percutaneous), renal parenchyma reserve, anesthesia (general versus sedation) and physician performing the procedure

(surgeon versus radiologist) can strongly influence these rates. Both ablative procedures appear to have minimal impact on renal function. Perfect assessment of the ablated tumours at postprocedural imaging is crucial for evaluating the adequacy of treatment and guiding further management. There is an urgent need for pre- and postoperative algorithms, strong, uniform and explicit indications and a standard consensus for follow-up schedules in the use of ablative therapies, which is nonexistent at this moment.

At this time, there is insufficient long-term data available to make adequate comparisons between ablative techniques. Therefore ablative therapies should be reserved for carefully selected high surgical risk patients with SRMs $< 4\text{ cm}$ (Grade C). The alternative option in many patients is active surveillance, which at the present seems to have a similar outcome (with all limitations of poor data) at clearly lower invasiveness and complications. This is also quite apparent in the meta-analysis used for the 2008 AUA Guidelines on SRMs [93,94].

To date, the use of other minimally invasive techniques, such as HIFU, radiosurgery, microwave thermotherapy, laser interstitial thermal therapy and pulsed cavitation ultrasound should be considered experimental. Further studies are required to determine their oncological and functional role in the management of localized RCC.

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VII. CONCLUSIONS - LIMITATIONS OF THE LITERATURE

The recent meta-analysis of Kunkle et al including 99 studies representing 6471 tumours illustrates that PN, cryoablation, RFA and active surveillance are viable approaches to the management of SRMs. Although long-term data have demonstrated excellent outcomes for PN, extended oncological efficacy remains to be established for thermal ablation and active surveillance. Compared with PN, current data demonstrate a significantly higher incidence of local tumour recurrence following cryoablation and RFA with cryoablation predominantly performed laparoscopically resulting in less local tumour progression than RFA generally performed percutaneously (RR 1.00, 7.45, 18.23, respectively). However, no statistical differences were detected in progression to metastatic RCC regardless of treatment option (PN, cryoablation or RFA) or absence of treatment (active surveillance) (RR 1.00, 1.24, 3.21, 0.11, respectively). These data raises concern over a possible overtreatment bias for SRMs [1]. Delayed intervention for SRMs appears to be a safe treatment strategy in selected patients [2]. Currently, no hard recommendations can be made against a given treatment modality for localized, SRMs because of the limitations of the current studies.

We identified the most important limitations of the existing literature on management of localized renal cell carcinoma. The main limitation seen across all treatment options was the lack of well-designed prospective or randomised studies. Selection bias (i.e. differences in patient age, tumour size and follow-up durations) is clear across interventions. For example active surveillance and ablative therapies generally have been performed selectively in older patients with smaller tumours and favourable radiographic findings. Other weaknesses include the absence of

transparent selection criteria, standardized technical application of the interventions, clear definitions of success and standardized methodical reporting of complications and other outcomes. Renal function was usually reported as pre- and posttreatment creatinine levels or as estimated glomerular filtration rate (eGFR) or creatinine clearance measurements from 24-hour urine collection. Furthermore, the lack of pathologic data in ablative and expectantly followed series remains a confounding factor when attempting to compare outcomes for renal lesions treated with other interventions. The category of tumours with unknown pathology certainly includes a number of benign tumours and thus, measures of treatment efficacy may be overestimated. Limited clinical follow-up of some studies may make their oncologic outcomes subject to follow-up bias. For example, some series of ablated lesions tend to include shorter post-treatment follow-up compared with published series of surgically managed or expectantly followed tumours. Reporting and publication biases probably also exist; studies with higher complication or recurrence rates or other poor outcomes tend not to be published. For example, few data regarding the morbidity of RN were published until the introduction of LRN. In addition, there is the problem of technique bias in the interpretation of the results. For example, percutaneous therapy is repeated without difficulty whereas laparoscopic therapy is not. This certainly influences the behaviour of the treating physician at the time of therapy.

In conclusion, the findings reported here must be interpreted within the context of the limitations outlined above. In order to allow better comparisons between treatment options for localized renal cell carcinoma, future research attempts should minimize these limitations by promoting prospective randomized evaluations.

VIII. EAU AND AUA STATEMENTS FOR TREATMENT OF LOCALIZED RCC

1. EAU STATEMENTS (UPDATE 2009)[3]

Surgical therapy is the only curative approach for the treatment of RCC. Routine extended lymph node dissection in patients without detectable lymph nodes does not improve survival and can be restricted to staging purposes (Grade A). Adrenalectomy, together with nephrectomy, except in the case of large upper pole tumours where direct invasion of the adrenal gland is likely, can be spared in most patients (Grade B). Embolisation as a palliative approach can be beneficial in patients unfit for surgery with massive hematuria or profound local pain (Grade C).

NSS is an established curative approach for the treatment of RCC (Grade B). NSS for tumours \geq

4-7 cm maximum diameter can be performed in centres with expertise in selected patients (Grade B). A minimal tumour-free surgical margin following partial resection of RCC appears appropriate to avoid the increased risk of local recurrence (Grade B). If tumours of larger size are treated with NSS, follow-up should be intensified due to increased risk of intrarenal recurrence (Grade B).

Laparoscopic tumour nephrectomy should be performed in centres with laparoscopic expertise (Grade B). Laparoscopic tumour nephrectomy is likely to become a widely distributed treatment option. It can be promoted in specialised centres treating kidney tumours (Grade B).

OPN currently remains the standard of care (Grade C). LPN should be limited to experienced centres (Grade C).

Currently, patients not suitable for OPN due to poor performance status with smaller peripheral tumours should be considered for non-surgical alternative techniques (Grade B).

These techniques include image-guided percutaneous and minimally invasive techniques, e.g. percutaneous RFA, cryoablation, microwave ablation, laser ablation and high-intensity focused ultrasound ablation (grade B).

2. AUA STATEMENTS 2008[4]

The statements are graded with respect to the degree of flexibility in application. A "standard" is the most rigid treatment policy. A "recommendation" has significantly less rigidity, and an "option" has the largest amount of flexibility.

For all patients

Standard: high quality cross-sectional imaging (CT or MRI) with and without contrast.

Standard: discuss the current understanding of the natural history of clinical stage 1 renal masses, the relative risks of benign vs. malignant pathology and the potential role of active surveillance.

Standard: percutaneous renal mass core biopsy with or without fine needle aspiration in all patients undergoing thermal ablation and in patients for whom, it might impact management, particularly patients with radiographic findings suggestive of lymphoma, abscess or metastasis.

Standard: review the available treatment options and the attendant benefits and risks, including oncologic considerations, renal functional considerations and potential morbidities.

Standard: counsel patients about potential advantages of NSS in imperative and elective settings (avoidance of the need for dialysis, reduced risk of developing CKD with attendant morbidity and mortality).

A healthy patient with a clinical T1a (≤ 4 cm) enhancing renal mass

Standard: PN

Alternate standard: RN when PN is not technically feasible

Option: thermal ablation but higher risk for recurrence

Option: active surveillance but small non-negligible risk for tumour progression

An elderly patient with major comorbidities and a clinical T1a (≤ 4 cm) enhancing renal mass

Standard: PN with increased surgical risk

Standard: RN with increased surgical risk

Recommendation: thermal ablation because less invasive in this high-risk patient

Recommendation: active surveillance with delayed intervention in this high-risk patient

A healthy patient with a clinical T1b (4.0 to 7.0 cm) enhancing renal mass

Standard: RN for patients with normal contralateral kidney

Standard: PN, particularly when there is need to preserve renal function

Option: thermal ablation but higher risk for recurrence

Option: active surveillance with delayed intervention but small non-negligible risk for tumour progression

An elderly patient with major comorbidities and a T1b (4.0 to 7.0 cm) enhancing renal mass

Standard: RN for patients with a normal contralateral kidney, but increased surgical risk and increased risk of CKD

Recommendation: PN when there is need to preserve renal function although increased urologic morbidity

Option: thermal ablation because less invasive in this high-risk patient but clearly higher risk for recurrence

Recommendation: active surveillance in this high-risk patient

IX. CONSENSUS REGARDING TREATMENT OPTIONS FOR LOCALIZED RCC

1. ACTIVE SURVEILLANCE

Active surveillance is an acceptable option for the treatment of SRMs that should be discussed with

all patients. **Active surveillance should be a first treatment option for SRMs < 4 cm in unfit patients or those with limited life expectancy (Grade C). Delayed intervention should be undertaken in tumours that show fast growth during active surveillance (Grade C).** Patients should be counselled about the small but non-negligible risk of tumour progression during the observation period, possible loss of the opportunity for nephron-sparing surgery, lack of curative salvage therapies if metastatic disease develops, limitations of renal mass biopsy, lack of long-term data on surveillance, close follow-up imaging and required compliance.

A significant number of SRMs (< 4 cm) are actually benign tumours (20%). No more than about 20 to 25% of SRMs have potentially aggressive characteristics. Several studies have shown increased aggressive potential of renal masses with a diameter > 3 cm. Data of surveillance series reveal that the majority of untreated localized renal tumours grow slowly and have little tendency to metastasize, at least in the first few years. Delayed intervention should be restricted to tumours that show fast growth during observation and have a higher risk of progression to metastatic disease. Renal mass biopsy enhanced by molecular profiling holds promise for assessing aggressive potential. Further research will be required to define the utility and limitations of this approach to improve the selection of patients for active surveillance. Larger tumours beyond a diameter of 3 or 4 cm, with aggressive behaviour and rapid growth are at risk of progression to metastatic disease and should be treated proactively.

2. PARTIAL AND RADICAL NEPHRECTOMY

Nephron-sparing surgery should be a primary consideration in all patients with localized SRMs. This is based on the information that PN of small renal tumours preserves as much normal renal parenchyma as possible, provides equivalent adequate oncologic outcomes as RN and is associated with a reduced risk of developing CKD compared with RN. Data have demonstrated that RN can result in a higher risk of CKD which is associated with increased risk of cardiovascular events and mortality. Partial nephrectomy is the reference standard for the treatment of SRMs, whether for imperative or elective indications. At present, PN is seriously underutilized while it is often feasible even for a centrally located tumour or a tumour in the renal hilum when performed by an experienced surgeon. Laparoscopic PN can provide faster convalescence, but initial LPN reports were associated with somewhat longer ischemia times and increased risk of postoperative hemorrhage compared to OPN. However the more recent data presented in this chapter demonstrates that these concerns are no longer valid, and that contemporary LPN outcomes are similar to contemporary OPN outcomes, given adequate minimally invasive expertise.

In patients with a clinical T1 renal tumour, PN provides equivalent local tumour control as RN, while minimizing development of new-onset CKD or worsening of existing CKD (Grade B). As such, PN is the established treatment for T1a tumours (< 4 cm) and an emerging standard treatment for T1b tumours (4 to 7 cm) provided that the operation is technically feasible and the tumour can be entirely and adequately removed (Grade B). Any tumour-free surgical margin following PN appears sufficient to prevent local recurrence and disease progression from RCC (Grade B).

RN remains a viable option in cases when PN is not technically feasible based on tumour size, location or radiographic appearance as determined by the urologic surgeon. When RN is required, laparoscopic RN should be considered as it is a recognized standard now. It is associated with low morbidity and faster return to normal activities, given adequate surgeon expertise. ***Therefore, LRN should be the standard of care for T1 and T2 tumours, provided that it is performed in an advanced laparoscopic centre by an experienced surgeon and NSS is not applicable (Grade B).*** Robotic-assisted partial nephrectomy is rapidly emerging as an alternative to LPN for the treatment of renal malignancy.

3. THERMAL ABLATION

Cryoablation and RFA are reasonable minimally invasive treatment options for most small (mainly < 3 cm) low grade renal tumours in patients who are at high surgical risk, who are not candidates for active surveillance and who accept the need for long-term radiographic surveillance after ablation. Percutaneous tumour core biopsy with or without fine needle aspiration should always be performed prior to ablation to define histology. Posttreatment biopsies may be necessary when recurrence or incomplete ablation is suspected. When deciding on thermal ablation, it is important to counsel patients regarding the slightly increased risk of local recurrence and the potential need for retreatment when compared to surgical excision. Counselling about thermal ablation should further include the absence of established radiographic measures of post-ablative success, the potential for difficult surgical salvage therapy due to perinephric fibrosis if tumour progression developed, and the substantial limitations of the existing literature on thermal ablation. Larger tumours beyond a diameter of 3 or 4 cm and those with irregular form or infiltrative growth pattern may be associated with increased risk of recurrence when treated with thermal ablative therapies.

At this time there is insufficient long-term data available to make adequate comparisons between ablative techniques. Therefore ablative therapies

should be reserved for carefully selected high surgical risk patients with SRMs < 4 cm (Grade C).

X. NEW RESEARCH – FUTURE DIRECTIONS

To allow comparison of the different treatment options for localized RCC, future studies should be prospectively designed, have identical selection criteria, standardized treatment protocols and consistent follow-up strategies using markers of clinical success and ideally be conducted in a randomised way [5]. In addition, as newer treatment options become available, future studies should include quality of life (QOL) and cost-efficacy outcomes [6].

The most widely used system to provide prognostic information for RCC is currently the tumour, nodes, metastasis (TNM) staging system. The recent detection of molecular tumour biomarkers is expected to refine the staging and prognostication of RCC. There is already evidence that gene expression profiles obtained with high throughput microarray technology can identify histological subtypes of RCC and predict clinical outcomes of the disease. Biomarkers will eventually improve our ability to predict the malignant potential of a tumour and to stratify patients into more sophisticated risk categories [7]. Further active surveillance series with long-term follow-up are required to determine the real risks associated with this approach. Molecular profiling of SRMs is now possible but the available data on molecular markers are not plentiful enough for general use in clinical practice. Research will be required to define the utility and limitations of renal mass biopsy enhanced by molecular profiling [8,9].

Further endeavours are required to clarify the long-term metabolic consequences of a decreased number of functioning nephrons following RN for RCC. This may result in a better understanding of the pleiotropic effects of CKD in patients treated with RN, and may offer a further rationale for the implementation of nephron-sparing strategies for the treatment of localized RCC. Moreover, novel protective measures to minimize ischemic renal damage (pharmacologic, immunologic) should be further examined in order to improve the feasibility and safety of nephron-sparing surgery [10].

The use of the DaVinci Robot for robotic-assisted LPN is currently being evaluated at specialized laparoscopic centres [11,12]. Since 2004, four centres have reported their experience with robotic-assisted LPN. Robotic-assisted LPN may potentially enable more urologists to perform LPN, thereby allowing wider dissemination of minimally invasive nephron-sparing surgery [12]. In addition, new developments such as single-port access laparoscopic surgery

and natural-orifice transluminal endoscopic surgery (NOTES) have received increased attention from the urological community. These techniques will continue to evolve and might lead to more advanced therapeutic options for minimally invasive renal surgery [13,14]. Novel surgical image-navigation system has also been emerged recently. Image-guided surgery is a new field in which visualization of the surgical anatomy beyond the surgical view helps the surgeon to enable percutaneous, laparoscopic, or robotic surgery more precisely and safely. Recent reports described the novel clinical capability of image-fusion system of ultrasonography (US) with computed tomography (CT) or Magnetic Resonance Imaging (MRI), real-time 3-dimensional US (3D US) navigation system, MRI-compatible navigation system, and augmented reality technology [15-18]. Digital-image-based computerized control of the surgical procedures has great potential to improve precision of tumour ablation/removal with maximizing of preservation of the renal function and surrounding healthy anatomy.

Major advances in the understanding of the molecular biology of RCC have led to the development of several new therapies that target ligands at the molecular level, so-called "targeted therapies". The molecular targets important in clear cell RCC include vascular endothelial growth factor (VEGF) receptors, the mammalian target of rapamycin, and the VEGF molecule itself. The small molecule tyrosine kinase inhibitors sunitinib and sorafenib, the mammalian target of rapamycin inhibitor temsirolimus and the combination of the monoclonal antibody bevacizumab with interferon-alpha are currently approved for treatment of metastatic RCC [19]. These new agents improve quality of life and seem able to stabilise metastatic RCC for a prolonged period of time [20]. Recently-reported and ongoing studies compare combination therapies with single agents and determine the efficacy of single agents as adjuvant therapy for higher-risk localized and locally-advanced disease. However, there is currently no role for targeted molecular therapy in the treatment of localized RCC outside of a clinical trial.

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XI. EVIDENCE TABLE

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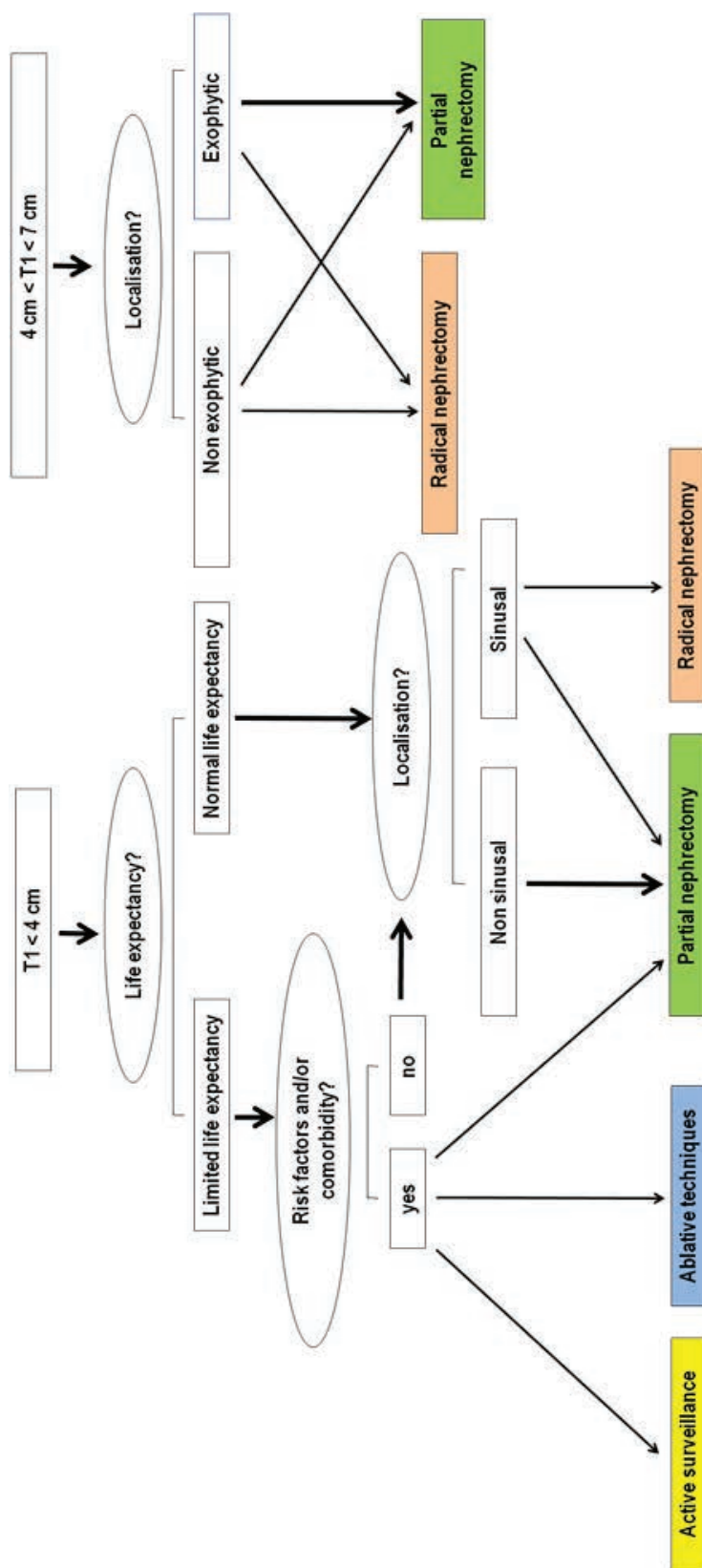
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Wang AJ, Bhayani SB. Robotic partial nephrectomy versus laparoscopic partial nephrectomy for renal cell carcinoma: single-surgeon analysis of >100 consecutive procedures. Urology 2009;73(2):306-310		3
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XIII. ALGORITHM RENAL T1TUMOURS

Adapted from the algorithm of Méjean et al, 2007

Arrows in font size are significant



Committee 6

Locally Advanced Disease

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III. THE ROLE OF LYMPH NODE DISSECTION AND MANAGEMENT OF NODAL METASTASES	VI. MANAGEMENT OF LOCAL RECURRENCE
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Locally Advanced Disease

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I. INTRODUCTION

Despite the increased detection of small, asymptomatic renal masses through the increased use of abdominal imaging for non-specific complaints or for non-renal malignancy staging evaluation, there remains a significant subset of patients that present with locally advanced and/or metastatic renal cell carcinoma (RCC). Regarding locally advanced RCC, these include patients with venous thrombi, extra-capsular and adjacent organ involvement, as well as nodal disease. Locally recurrent RCC after definitive surgical therapy should also be included in this group of patients. The surgical management of these patients can be extremely daunting and complex and despite expert surgical management, many are destined to suffer relapse, either locally, distantly, or both[1]. In concert with surgical management of these locally advanced tumors, clinical research efforts have focused on the development of effective adjuvant and/or neoadjuvant therapy that can effectively reduce the risk of disease recurrence following surgical extirpation. Sadly, effective adjuvant/neoadjuvant therapy does not exist for renal cell carcinoma in the year 2010, despite the conduct of many phase III clinical trials testing agents that have shown promise in the setting of metastatic disease[2, 3]. Currently, the new targeted therapies are being tested in both the adjuvant and neoadjuvant setting for locally advanced renal cell carcinoma, and we anxiously await the results of these important ongoing clinical trials.

In this article, we will discuss the management and outcomes for patients who present with locally advanced RCC, focusing specifically on the management of renal vein and inferior vena cava

thrombi, the role of lymph node dissection and the management of nodal metastases, the management of adjacent organ invasion, the management of local recurrences in the absence of metastatic disease, and the role of adjuvant and neoadjuvant therapy. We will present lessons of evidence for each of our findings, and a consensus statement derived from further deliberation by committee members.

II. VENOUS INVASION

Approximately 10% of patients with RCC have venous tumor thrombus in the renal vein (RV) or inferior vena cava (IVC) with approximately 1% having tumor thrombus extending up to the right atrium.[4] (Fig.1) Venous tumor thrombus patients require more meticulous care than many other RCC patients secondary to the associated risks and complications including venous congestion, embolic events, and the possibility of thrombosis with bland blood clot. Furthermore, proximal progression of tumor thrombus secondary to delay in management increases complexity and potential morbidity of surgical resection.[5, 6]

1. EVALUATION

Appropriate management of RCC with tumor thrombus requires accurate staging. Enhanced magnetic resonance imaging (MRI) has been determined to be the most reliable method of imaging tumor thrombus extent, involvement of vein tributaries, detection and differentiation of tumor thrombus versus blood clot, and assessing for vessel occlusion.[7] Recently, multidetector computerized tomography (CT) has been shown to correlate well with intraoperative findings including extent of thrombus as well as pathological findings at the time

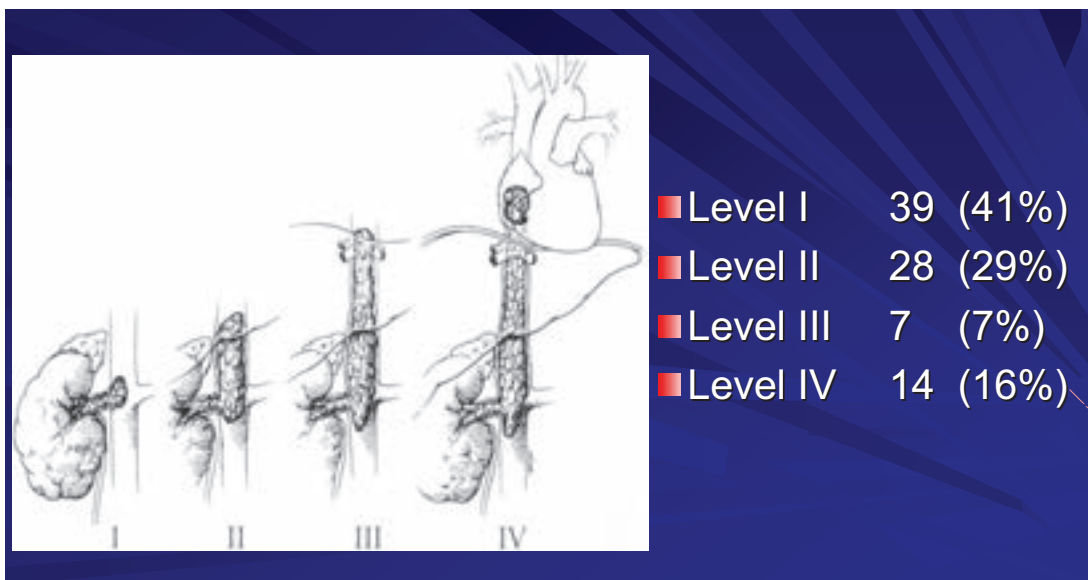


Fig. 1: Level of Tumor Thrombus

of resection of RCC with tumor thrombectomy. [8] Due to possible rapid progression of tumor thrombus, operative management should be preceded by very recent imaging. Staging for bony, abdominal, thoracic, and intracranial metastatic involvement should follow standard protocols.

2. MANAGEMENT

Case reports of tumor thrombus downstaging with targeted agents indicate that neoadjuvant therapy may become a viable approach.[9-11] However, until further data is available this practice should be limited to clinical trials. **(level of evidence: 4)** Until such data are available, therapy for the patient with tumor thrombus is based upon surgical resection of the primary tumor along with the entire burden of intrascalar tumor thrombus. Some data from case cohort series indicate that surgical management of RCC with tumor thrombus may provide superior survival to non-surgical management (median of 19.8 versus 6.9 months, respectively).[12] However, the cohorts were significantly different with higher tumor burden in the non-surgical group.

A recent retrospective review of a large case series provides an excellent guide to management based on tumor thrombus level.[5] **(level of evidence: 3b)** Operative management is dictated primarily by the extent of the tumor thrombus. Isolation of the ascular structures is the initial step in dissection. Ligation of the ipsilateral renal artery is the first step and is best accomplished by approaching the aorta directly for both left and right tumors. Preoperative angioembolization is not recommended and was shown to offer no advantage in a large case control series and was associated with increased

complications.[13] After arterial ligation the next step is venous control and excision of thrombus. Ligation of minor tributaries to the IVC including some lumbar and minor hepatic branches may be necessary to provide adequate hemostasis and tumor visualization during tumor excision.[5] However, in cases of complete or near complete occlusion, meticulous dissection of all collateral veins is to be avoided as these represent the majority of venous return and are needed to maintain preload until the IVC can be cleared. Minimal manipulation of the kidney and tumor reduce the risk of embolization and therefore the nephrectomy is completed after excision of the thrombus.

For thrombus that is confined to the renal vein or just entering the IVC (which can be retracted back into the renal vein) minimal modification to standard approaches to open radical nephrectomy are required to assure complete removal of thrombus with negative margins.[5] Several reports of successful minimally invasive approaches to such low level thrombus have been published.[14-16]

Thrombus that is above the renal vein ostium and below the hepatic veins can be managed with occlusion of the venacava above and below the thrombus as well as occlusion of the contralateral renal vein. Such cases rarely require bypass. Excision of the thrombus en bloc with the ipsilateral renal vein and tumor is accomplished via a venotomy on the anterior IVC and including the ostium of the ipsilateral renal vein. The interior of the IVC should be flushed and inspected to assure complete clearance of tumor.[5]

Thrombus at the level of the hepatic veins and

below the diaphragm may require bypass but can be performed with simple occlusive measures in many cases.[5] The use of intraoperative transesophageal sonography can be very helpful for monitoring hemodynamics and assessing the thrombus. Excision of thrombus is accomplished with occlusion of the inflow to the liver (Pringle maneuver) along with control of the IVC below the thrombus as well as above the liver and control of the contralateral renal vein with a venacotomy which ends infrahepatically. After excision of the thrombus, the IVC can be clamped infrahepatic and the suprahepatic clamp can be released to allow restoration of flow to the liver.

Thrombus above the diaphragm necessitates opening the right atrium with simultaneous manipulation of thrombus from above and via an infrahepatic venacotomy below to assure complete clearance. Several case series support the use of bypass techniques including venovenous bypass and cardiopulmonary bypass with or without circulatory arrest.[17-20] The decision to use bypass is dependent upon the extent of occlusion of the IVC preoperatively as well as hemodynamics upon clamping the vascular structures intraoperatively. A recent large case series reported the use of some bypass technique in 100% of cases of thrombus above the diaphragm, 29% of cases below the diaphragm and within the intrahepatic IVC, and in only 2% of IVC thrombus cases that were below the liver.[5] In all cases involving the IVC complete clearance of adherent or invasive tumor thrombus may require complete or partial resection of the venacava and reconstruction with a patch or graft. Prevention of embolization of distal blood clot may require interruption of the venacava, or placement of an IVC filter.[21]

3. ONCOLOGIC OUTCOMES

The prognostic significance of the level of tumor thrombus has been evaluated extensively.[5, 22-31] (level of evidence: 3b) Most of these case series do not find a difference in survival based on level of tumor thrombus within the IVC. A recent retrospective review of 422 patients with pT3b RCC evaluated the cancer specific survival based on level of tumor thrombus.[24] Patients with IVC tumor thrombus were significantly more likely to die from RCC compared with patients with tumor thrombus confined to the renal vein even after adjusting for regional lymph node involvement and distant metastases.[24] The presence of renal venous wall invasion by tumor thrombus has been reported to be associated with poor prognosis relative to patients without wall invasion.[30]

Tumor specific features that are associated with diminished survival are similar to RCC without venous involvement and include presence of fat

invasion, lymph node involvement, metastases, histologic tumor necrosis, sarcomatoid features, and high tumor grade.[5] Median survival among 503 patients with clear cell renal cell carcinoma treated with surgery and no adjuvant therapy in a large retrospective review was 3.1 years with 5 year survival of 59% for patients without metastases and negative lymph nodes.[5]

Recommendations	Grade
• Enhanced MRI or multidetector CT provide important anatomic information regarding the magnitude of the tumor thrombus extension, necessary for staging, prognosis and surgical planning	A
• Up-front surgical therapy with radical nephrectomy and complete tumor thrombectomy should be performed in appropriate surgical candidates	A
• Routine renal arterial thromboembolization prior to radical nephrectomy is not advocated	B
• Oncologic outcomes after radical nephrectomy are driven by established prognostic features of the primary tumor rather than the extent of the venous thrombus	B

III. THE ROLE OF LYMPH NODE DISSECTION AND MANAGEMENT OF NODAL METASTASES

The potential therapeutic benefits of lymph node dissection (LND) at the time of radical nephrectomy (RN) are two-fold. First, the removal of regional nodal metastases can provide cure in patients whose disease is confined to the retroperitoneum, concurrently allowing appropriate selection of these high-risk patients to receive adjuvant systemic targeted therapy in the context of a clinical trial. Alternatively, regional LND in patients with systemic micro- and macro-metastatic disease may provide sufficient cytoreduction to improve therapeutic efficacy and tolerability of post-surgical systemic treatments.

1. LOCALLY ADVANCED RCC

Several contemporary series demonstrate that aggressive removal of regional nodal metastases translates into improved cancer specific survival and provides long term cures in a significant number of patients.[32-34] (level of evidence: 3a). Pantuck et al, found that 43 RCC patients with clinically

suspected nodal involvement, without distant metastases, who underwent some form of LND, demonstrated a 5 month improvement in median survival, compared to patients in whom clinically positive LNs were left in situ at the time of RN.[32] Moreover, LND dissection was an independent predictor of survival in their multivariable analysis. Investigators from M. D. Anderson Cancer Center reported outcomes of 40 patients with regional nodal involvement without evidence of systemic metastatic disease, all of whom underwent complete extended LND.[33] Only cases in which all gross disease was completely removed were considered successful resections and included in the final analysis. Median cancer specific survival was 20.3 months and 30% of patients had no evidence of disease at a median follow-up of 18 months.[33]

In contrast to the data presented above in the setting of clinically positive LN's, numerous retrospective studies have found no therapeutic benefit of routine LND in the setting of the lack of clinically suspicious lymphadenopathy. The only randomized prospective clinical study to evaluate the role of routine lymphadenectomy at the time of RN for RCC was conducted by European Organization for Research and Treatment of Cancer (EORTC 30881).[35] In this trial, 772 patients with clinical T1-3N0M0 RCC were randomized to RN only or RN and lymph node dissection. RN was performed with or without removal of retroperitoneal tissue from the crus of the diaphragm to the bifurcation of the aorta. Although proponents of LND argue that the study has not reached maturity, preliminary results from the randomized trial failed to demonstrate any significant differences in cancer-specific survival between the study groups (**level of evidence: 1b**). Due to high prevalence of low risk RCC, this study was significantly underpowered to detect a survival advantage afforded by LND. Not surprisingly, only 3% of patients who underwent lymph node dissection at the time of RN had lymph node metastases, and very few patients (17%) progressed or died from RCC, thus making it extremely difficult to draw conclusions about the therapeutic efficacy of lymph node dissection in RCC.[35] (**Fig. 2,3**)

2. METASTATIC RCC

Studies that have evaluated the role of LND at the time of cytoreductive RN for metastatic RCC also support aggressive debulking of regional nodal disease in addition to cytoreductive RN (**level of evidence: 3a**). Vasselli and colleagues, at the National Cancer Institute, evaluated a cohort of patients treated with cytoreductive RN and IL-2 immunotherapy and compared 82 pathologically node negative patients with 72 similar patients who had pathologically confirmed involvement of regional LNs.[36] Not surprisingly, these authors found a

median survival of 14.7 months and 8.5 months, in node negative and positive groups, respectively ($P = .0004$). There was no statistical difference in survival between patients with node positive disease who underwent complete nodal dissection and patients with pN0 disease. Similarly, in a report describing the UCLA experience with 129 patients with grossly positive lymph nodes and systemic metastases, the median survival after IL-2 immunotherapy was approximately 5 months longer for patients who underwent LND compared to those who did not.[32]

3. PATIENT SELECTION FOR LYMPHADENECTOMY

Realizing the limitations of current radiologic imaging techniques, a rational approach for identification of patients at high risk of harboring sub-clinical LN metastases was reported by the Mayo Clinic group.[37] Their analysis of more than 1,600 patients with clear cell renal cell carcinoma identified five histological features that placed patients at increased risk for regional lymph node metastases: high stage, high nuclear grade, large size, a sarcomatoid component, and presence of histological tumor necrosis. In their protocol, the authors established a "risk cut point" of two features as a threshold for placing a patient at significant risk of regional lymph node involvement, if present (**Table 1**). Similarly, a pre-surgical prognostic nomogram for prediction of regional nodal metastases was developed based on 139 (2.9%) node positive patients out of the 4,844 patients who underwent RN at the Mayo Clinic and Memorial Sloan Kettering Cancer Center.[38] The nomogram utilized age, gender, performance status, co-morbidity index, symptoms at presentation, radiologic lymphadenopathy, tumor size and location, presence of necrosis, pre-operative hemoglobin, and history of hematuria to predict the probability of pathologically positive LN with an accuracy of 76.1%.[38] If validated in external patient cohorts, these predictive tools could serve as a valuable guide to selectively target patients for extended LND at the time of RN.

To date, there are no uniformly accepted guidelines on the extent or anatomic boundaries of LND when performed as an adjunct to RN for RCC. Available data, however, suggests that a more thorough LND provides a significant improvement in staging accuracy.[39, 40] Based on these findings and the knowledge gained from the classic renal lymph node mapping studies, para-aortic dissection from the crus of the diaphragm to the bifurcation of the aorta is performed for the left sided tumors; however, for the right sided tumors both para-caval and inter-aortocaval dissection from the diaphragmatic crus to the bifurcation of the great vessels is recommended.[41] (**level of evidence: 4**)

TABLE 1. The Mayo Clinic risk factors for prediction of regional nodal metastases in RCC.[37]

Feature	OR (95% CI)	p
Grade 3 + 4	5.25 (1.99-13.82)	<0.001
Sarcomatoid component	4.11 (2.08-8.12)	<0.001
Tumor 10 cm or greater	2.17 (1.27-3.70)	0.005
Primary stage pT3 + pT4	2.00 (1.13-3.55)	0.017
Histological tumor necrosis	1.86 (1.00-3.48)	0.051
No. Features	No. pN0/pNx (%)	No. pN1/pN2 (%)
0	726 (99.6)	3 (0.4)
1	299 (99.0)	3 (1.0)
2	264 (95.7)	12 (4.4)
3	183 (87.6)	26 (12.4)
4	105 (86.8)	16 (13.2)
5	7 (46.7)	8 (53.3)

- Randomized phase III trial of RN alone or with complete lymph node (LN) dissection showed no benefit of dissection

Group	N	Metastasis Rate Within Group
All patients	772	3.3%
Patients in LN dissection arm without palpable LN	299	1%
Patients in LN dissection arm with palpable LN	43	16%
Patients in RN-only arm with palpable LN at surgery	29	21%

Blom JH et al. *Eur Urol.* 1999;36:570.

Fig. 2: Result of the EORTC 30881: Lymph Node Dissection in Localized RCC

		Without lymph-node dissection		With complete lymph-node dissection		p value
			%	n	%	
Death			1	4	1	0.87
Local relapse			5	21	6	0.31
Distant relapse						0.81
Local or distant relapse	T2	230	pT category	n	63	
Progression-free survival	T3	96	T0	5	29	0.70
Progression-free survival	T4	2	T1	19	1	0.84
Second primary	TX	2	1	3	1	0.28

Blom et al., *Eur Urol.* 2008

Fig. 3: Result EORTC 30881: Lymph Node Dissection in Localized RCC

Recommendations	Grade
• No therapeutic benefit of retroperitoneal lymphadenectomy has been demonstrated in patients without clinical evidence of lymphadenopathy	A
• Removal of gross regional nodal metastases can result in improved cancer specific survival in and can provide long term cure	B
• When indicated, para-aortic dissection from the crus of the diaphragm to the bifurcation of the aorta is performed for the left sided tumors; for the right sided tumors both para-caval and inter-aortocaval dissection is necessary	C

IV. ADJACENT ORGAN INVASION

RCC may rarely present with locally advanced disease, in the absence of distant metastatic disease, with reported prevalence of approximately 1-1.5% at centers such as MSKCC and MDACC, as well as the SEER registry.[42-44] The incidence of advanced tumors has increased over time.[45] AJCC staging of kidney cancer describes T4 RCC as that which has penetrated beyond Gerota's fascia to ascending colon or duodenum from the right kidney, descending colon from the left kidney, diaphragm, peritoneum, tail of pancreas, psoas muscle, ribs, liver, spleen, stomach, aorta, or contralateral kidney, adrenal gland, or ureter, and is Stage IV disease. Earlier reports in the literature were routinely pessimistic about the value of surgical resection for such advanced disease, but this important issue has been recently revisited in several publications. It is important to note that all such studies are case series or retrospective cohort studies (level of evidence 4 and 2b, respectively).

The first modern data on this patient population is from MDACC.[42] 30 patients out of an institutional database of over 3000 patients over a 15 year accrual period, were identified as having T4NxM0 RCC and underwent complete resection of the primary tumor, with adjacent organ resection, all with negative surgical margins. The most common sites of resection were colon, pancreas and diaphragm, although liver, spleen and bowel mesentery invasion were also seen. No reliable preoperative predictors of invasion were identified. Of the important messages in this report, perhaps the most important, was that 60% of patients thought to have T4 disease were downstaged to <pT4 disease, including 2 patients who were found to only have pT2 disease. On multivariate Cox regression analysis the only predictors of survival was the presence

of pT4 disease and most importantly, lymph node metastases (RR 17, $p=.002$) with 3 year overall survival of 66% in LN negative patients versus 12% in lymph node positive patients, which comprised a third of patients. This report concluded that actual pathological involvement from RCC is rare, and not reliably predicted from preoperative or intraoperative findings. Most patients are clinically overstaged. These surgeries are possible to perform with acceptable patient morbidity (mean length of stay 9 days, range 4-22) and no perioperative deaths.

Another valuable study on this rare patient subset was from MSKCC. Instead of looking at patients with clinically suspected locally advanced renal cancer invading other organs, this group looked at 38 patients out of a total of approximately 2500 patients who had pathological T3 or T4 disease with resection of adjacent organs or structures. Approximately one quarter had positive lymph nodes. Most patients had negative pathologic margins, but 36% had a positive margin. Presence of a positive margin was significantly associated with decreased survival ($p = .006$). 89% of patients died with a median survival of 11.7 months (range 5-29). A final study from South Asia studied 18 patients with RCC suspicious for adjacent organ involvement. Similar to the report from MDACC, although less frequent, 3/18 patients did not have true organ invasion on the final resection specimen. Interestingly, while 15 patients died at a median duration of 7.5 months, 3 patients were still alive at a median of 13, 16 and 25 months. There were no differences identified in terms of patient, tumor and laboratory variables between those patients who lived and those who died. Lacking from this particular series was any description of nodal pathology.

In an effort to understand the important issue is whether the results of radical nephrectomy for T4 renal cancer combined with adjacent organ or structure extirpation is confined only to true centers of expertise, and the important question of what happens to patients if surgery is not performed. Capitanio examined 310 patients with clinical T4N0-2 RCC in the SEER registry, which is thought to be representative of the US population, who underwent resection (246) or no surgery (64). Those who underwent surgery had a median survival of 48 months compared to only 6 months for those who underwent no surgery (Hazard ratio of 2.2). The effect of surgery for those patients (125) who had T4N0 disease was even stronger, with a hazard ratio of 3.7, with a cancer specific mortality of approximately 40% at 10 years, even after controlling for other cause mortality, which might be expected (MI, stroke) after this kind of extensive surgery. No benefit was seen in those patients with node-positive disease. As an important caveat for the community urologic surgeon, the study was confounded by only studying

9 SEER regions (out of 17), and four of these regions contained academic medical centers with significant urologic oncology expertise.

Thus, it may be prudent for patients with this kind of disease to be cared for in centers where a true multidisciplinary team of surgeons familiar with this kind of resection, and of subsequent reconstruction (hepatobiliary, pancreatic, colorectal, a scular, body wall) may be present. In summary, in patients fit to undergo surgery with no clinical evidence of metastatic disease, and no evidence of pathological retroperitoneal adenopathy, rather than deeming patients with clinical T4 not curable or unresectable, and offering palliative treatment only, surgery is likely to be of benefit.

Unanswered questions remain which concern patient selection before committing a patient to extensive surgery, particularly the role of preoperative / postoperative prognostic factors, including serum biomarkers, and of the role of neoadjuvant targeted agent chemotherapy.[46] It is possible that the use of these newer chemotherapeutic agents be used in conjunction with surgical exploration of localized disease. Multi-institutional registries may be of value in trying to evaluate such outcomes.

Recommendations	Grade
• Adjacent organ invasion by RCC is not reliably predicted by preoperative radiologic imaging or intraoperative findings	C
• Appropriate surgical candidates should be managed with radical nephrectomy and en-bloc removal of adjacent tissue or organs if direct invasion is suspected	C

V. ADJUVANT/NEOADJUVANT (PRE-SURGICAL) THERAPY FOR RENAL CELL CARCINOMA

1. ADJUVANT THERAPY

While surgery remains the curative for the vast majority of patients with locally advanced renal cell carcinoma, there remains a significant population of patients that remain at high risk for disease relapse, both locally and distantly, after definitive surgical therapy. A large focus of clinical research in renal cell carcinoma has been the development of an effective adjuvant therapy to decrease risk of recurrence and improve survival in patients at high risk for relapse after surgery. Logically, therapeutic development in the adjuvant setting has focused on therapy with

some evidence of activity in the setting of metastatic disease. To date, in the year 2010, effective adjuvant therapy does not exist for renal cell carcinoma.

Initial phase III randomized clinical trials focused on hormonal therapy such as medroxyprogesterone acetate in the adjuvant setting. These studies demonstrated significant toxicity associated with adjuvant therapy and no recurrence free or overall survival benefit for the treatment arm[47, 48]. (level of evidence: 1b) In addition, adjuvant radiation therapy has been studied and may decrease the risk of local recurrence but had no impact on the occurrence of distant metastases or survival[49]. (level of evidence: 3a) With the development and implementation of immunotherapy for the treatment of metastatic renal cell carcinoma, clinical research focused on the utility of this treatment modality in the adjuvant setting. Numerous phase III clinical trials have studied interferon and interleukin 2, either alone or in combination with various chemotherapeutics, in the adjuvant setting. To date, none have demonstrated a benefit regarding recurrence free or overall survival for patients[2, 3, 50-55]. (level of evidence: 1a) Immunotherapeutic strategies in the adjuvant setting have also focused on various vaccine formulations. The attraction of vaccines in this setting is that they are relatively non-toxic and rely on a competent host immune system for their anti-tumoral activity. While some, such as ivtespen, have shown evidence of activity in subset analyses focused on specific patient populations, none of the clinical research performed with a wide variety of vaccine formulations in the adjuvant setting can support their implementation into clinical practice at the current time[56-61]. (level of evidence: 1a) The antiangiogenic agent thalidomide has also been evaluated in the adjuvant setting for renal cell carcinoma, but like all other agents that demonstrated some modicum of activity in the metastatic setting, no benefit was seen in the adjuvant setting[62]. (level of evidence: 1b) A phase III clinical trial examining the role of the antibody G250 (ARISER), which targets the carbonic anhydrase IX protein and induces antibody dependent cellular cytotoxicity, has recently completed accrual but the results of this study have not been reported in the literature to date[2].

With the introduction of small molecule targeted therapy, such as the tyrosine kinase inhibitors sunitinib and sorafenib, in the treatment of metastatic renal cell carcinoma, there has been great excitement about the potential activity of these agents in the adjuvant setting. Currently, there are three large phase III randomized placebo controlled trials examining the activity of these agents in the adjuvant setting (Table 2). These include the ASSURE trial (ECOG 2805), where patients are randomized to 1 year of sorafenib or sunitinib versus placebo, the S-TRAC trial, where patients are randomized to 1 year of sunitinib versus

placebo, and the SORCE trial, where patients are randomized to 3 years of sorafenib or 1 year of sorafenib versus placebo[3, 63, 64]. While these trials remain ongoing at present, there have been significant concerns raised regarding the toxicity of these agents in the adjuvant setting. In fact, several modifications and amendments have been made to these trials, including dose reductions and increases in accrual goals, to help account for the not insignificant patient dropout rates related to drug intolerance[2, 65].

2. NEOADJUVANT THERAPY

There have been no randomized clinical trials examining the role of neoadjuvant therapy in the treatment of renal cell carcinoma. In fact, until very recently, the only modality studied in the neoadjuvant setting has been the issue of preoperative embolization prior to nephrectomy[66, 67]. **(level of evidence: 3a)** In these retrospective non-randomized studies, there is a suggestion that patients who had renal artery embolization prior to nephrectomy had a better overall survival relative to those that underwent nephrectomy alone. These findings have not been confirmed prospectively.

Prior to the development of targeted therapy, an axiom in the management of patients with renal cell carcinoma was the fact that the primary tumor rarely, if ever, demonstrates a reliable response to systemic therapy[68, 69]. **(level of evidence: 4)** This, in part, served as the impetus to perform cytoreductive nephrectomy in the management of metastatic disease. With the increased utilization of targeted therapy in the setting of metastatic renal cell carcinoma, anecdotal case reports and small single institutional series of patients treated with their primary tumor in place, demonstrating impressive responses in the primary tumor, began to appear in the literature[11, 46, 70]. **(level of evidence: 4)** These impressive responses have prompted a re-evaluating of the concept of neoadjuvant or presurgical therapy in both locally advanced and metastatic renal cell carcinoma. In an initial report of 17 patients treated with sunitinib with their primary tumor in place, Van der Veldt and colleagues reported that 23% of patients had a response as defined by RECIST criteria, and the mean volume of tumor reduction in the primary tumor was 31%. Subsequently, however, initial phase II studies suggest that pre-surgical targeted therapy is safe, but reliable and significant primary tumor downstaging or downsizing is uncommon with the current generation of targeted agents[46, 71-75]. **(level of evidence: 2b)** In the majority of these studies, the primary tumor demonstrated little if any response to systemic therapy prior to surgery. Dramatic reductions in tumor size, and thankfully, dramatic progressions in disease, were rare events. Currently, phase II and III studies are planned to further evaluate the role of targeted agents in the

neoadjuvant setting for both locally advanced and metastatic renal cell carcinoma (Table 2). (Fig. 4,5)

Recommendations	Grade
• Neoadjuvant or adjuvant therapy for RCC remains experimental	A
• Neoadjuvant targeted therapy prior to surgery is safe, however degree of cytoreduction is unpredictable and oncologic efficacy is not established	B

VI. MANAGEMENT OF LOCAL RECURRENCE

Local recurrences within the renal fossa can represent recurrent disease within the adrenal gland, the retroperitoneal lymph nodes, or the soft tissue tissues in the area of the prior renal tumor. While recurrence within the adrenal or retroperitoneal lymph nodes represent metastatic progression, recurrence in the soft tissues may represent a locally aggressive tumor but may also reflect the results of a surgical mishap with tumor violation at the original nephrectomy. Isolated local recurrence without evidence of distant metastases is a rare event, with a reported incidence of 1-2% following radical nephrectomy with curative intent[76-79]. As such, the lessons of evidence regarding natural history and methods of management are Level 4 at best.

Overall, the management of renal fossa recurrence is predominately surgical. All of the case series reported in the literature advocate aggressive surgical resection for a local recurrence in the absence of metastatic disease[76-79]. **(level of evidence: 4)** Esrig et al. reported on 10 patients who underwent surgical resection of locally recurrent renal cell carcinoma in the absence of metastatic disease[77]. In this series, 4 of 10 patients achieved durable disease free survival following surgical resection, with one patient without evidence of disease 18 years after surgery. In the series by Tanguay et al., 15 of 16 patients underwent complete surgical resection of locally recurrent disease, with 3 patients having positive surgical margins[78]. The authors found that those patients treated with neoadjuvant and/or adjuvant interferon therapy were twice as likely to remain without evidence of disease following surgery. Itano et al. reported on 30 patients in the Mayo Clinic experience with local recurrence[79]. Of these 9 were treated with observation, 11 were treated with therapy other than surgery, and 10 were treated with surgery alone or in combination with other therapies. With a median followup of 3.3 years, the authors found that patients who underwent aggressive surgical resection had a 5-year cause specific

TABLE 2. Ongoing clinical trials of neoadjuvant and adjuvant systemic therapy in patients with locally advanced RCC.

Trial/Institution	Design	Therapy
Neoadjuvant		
UT MD Anderson	Phase II	Axitinib
UT Southwestern	Phase II	Erlotinib
Adjuvant		
ARISER	Phase III	mAb G250 vs. Placebo
ASSURE	Phase III	Sunitinib vs. Sorafenib vs. Placebo
S-TRAC	Phase III	Sunitinib vs. Placebo
SORCE	Phase III	Sorafenib vs. Placebo

TABLE 3. Features predictive of systemic disease relapse after surgical resection of local RCC recurrence.[76]

Feature	OR	95% CI	p
Positive surgical margin after resection of local recurrence	3.207	1.065-9.654	0.038
Size of recurrent tumor	1.340	1.175-1.529	0.001
Presence of sarcomatoid features in recurrence specimen	11.648	4.000-33.921	0.001
Abnormal serum alkaline phosphatase at the time of recurrence	13.754	3.066-61.694	0.001
Abnormal serum lactate dehydrogenase at the time of recurrence	17.089	4.144-70.479	0.001

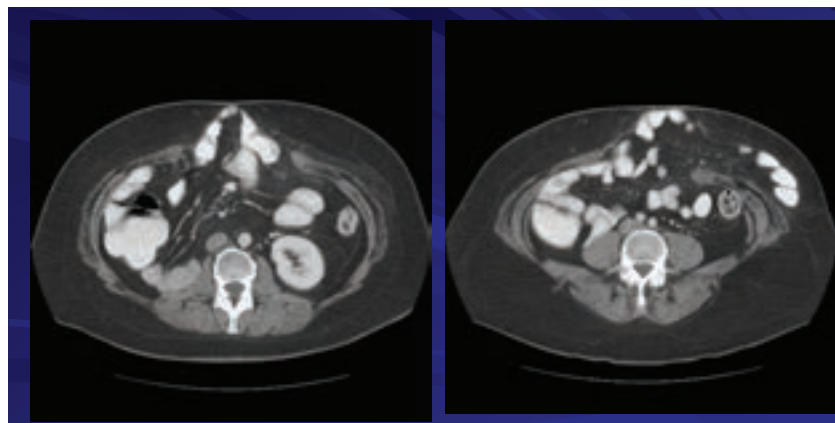


Fig. 4: Possible complication in wound healing by pre-surgical targeted therapy

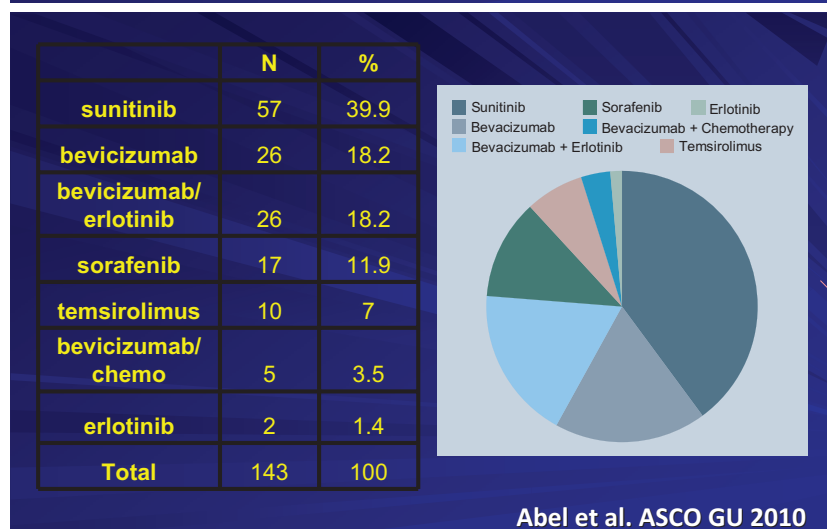


Fig 5. : Impact of Targeted Therapy On The Primary Tumor

survival of 51%, as compared to 18% with therapy other than surgery, and 13% with observation alone. Finally, Margulis et al reported on 54 patients with renal fossa recurrence treated with surgery, which represents the largest single institutional series in the literature[76]. Of these, 69% underwent perioperative adjunctive systemic therapy. The authors identified 5 factors associated with a worse prognosis after surgical resection, including size greater than 5 cm, the presence of sarcomatoid dedifferentiation, a positive surgical resection margin, elevated alkaline phosphatase, and elevated lactate dehydrogenase (Table 3). Patients with none of these risk factors demonstrated a cancer specific survival of 111 months, whereas patients with more than one of these risk factors had a cancer specific survival of only 8 months.

In the absence of metastatic disease, aggressive surgical resection, either alone or in combination with perioperative (neoadjuvant +/- adjuvant) systemic therapy appears to provide the best outcomes for locally recurrent renal cell carcinoma. Limited data are available on the efficacy of the new targeted agents in this setting, should be considered preoperatively if any of the adverse features identified by Margulis et al. exist.

Recommendations	Grade
• Surgical extirpation remains the standard of care for patients with isolated local recurrence of RCC	C
• Clinical prognostic factors can be utilized for experimental integration of perioperative systemic therapies in patients at high risk of disease relapse after surgery	C

VII. SUMMARY

The management of locally advanced RCC remains a daunting, surgically demanding endeavor but can be associated with excellent outcomes. With the exception of the role of lymph node dissection and adjuvant therapy in patient management, the vast majority of treatment recommendations are made based on level 3 and level 4 evidence. In fact, despite level 1 evidence to the contrary, the authors would still advocate lymph node dissection, even in the presence of clinically negative lymph nodes, to provide more accurate staging information and the potential to eliminate micro-metastatic disease. The development of effective adjuvant and neoadjuvant therapy remains the single greatest challenge in improving the outcome of patients with locally advanced disease.

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Treatment of Metastatic Disease

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Treatment of Metastatic Disease

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I. INTRODUCTION

Renal cell carcinoma (RCC) accounts for 2% of all cancers. In Europe, 40,000 patients are diagnosed with RCC each year, leading to 20,000 deaths [1].

One-third of patients are initially diagnosed with locally invasive or stage IV disease. Recurrence occurs in about 25% of patients having surgical resection for localized disease even though it was considered as curative. The prognosis for patients with distant disease is generally poor, with a 5-year survival rate not exceeding 10% [2]. Until the past 4 years, systemic treatments in patients with metastatic RCC (mRCC) have proven largely ineffective. Regarding chemotherapy or hormonal therapy, no single agent has been reported to achieve a consistent response rate in more than 10% of patients [3]. Only a very small percentage of patients are likely to develop long-term disease-free survival following interferon- α (IFN) and/or interleukin-2 (IL-2) based therapy [4-5]. At Memorial Sloan Kettering Cancer Center (MSKCC), the overall median survival in 670 patients who were treated with chemotherapy or immunotherapy in 24 consecutive clinical trials from 1975 to 1996 was 10 months [6].

Two pathways are essential to the pathophysiology of the clear cell RCC subtype: the hypoxia response pathway associated with inactivation of the von Hippel-Lindau (VHL) tumour suppressor gene and the mTOR (mammalian target of rapamycin) signaling pathway [7]. Several therapies, targeting these two pathways including sunitinib, sorafenib, temsirolimus, bevacizumab and everolimus are available for clinical use and have revolutionized the treatment of mRCC [8]. This article reviews current targeted treatment approaches in the first- and second-line mRCC settings, as well as modifications

to existing treatment algorithms, based on recently available data.

II. EVIDENCE ACQUISITION

Medical literature was retrieved from PubMed up until December 2009. Additional relevant articles and abstract reviews were included from the bibliographies of the retrieved literature. All data was reviewed and final statements were approved by experts in the field.

III. EVIDENCE SYNTHESIS

1. CURRENT TREATMENT APPROACHES UTILIZING NOVEL TARGETED AGENTS

At present, treatment for metastatic clear cell RCC with molecularly targeted agents can be broadly divided into the following categories: previously untreated patients, those refractory or intolerant to immunotherapy, and those who have failed treatment with VEGF-targeted therapy [2]. An important consideration that influences treatment decisions is the Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic risk stratification system, which is widely used to define patient profiles and provides an indication of overall survival (OS) [6]. In this system, derived from patients treated with interferon-based therapy on six prospective clinical trials at a single center in the US, five prognostic factors are used to categorize patients with mRCC into three risk groups: favorable (0 risk factors), intermediate (1-2 risk factors) and poor (≥ 3 risk factors). Median OS times for patients with good risk is 30 months, intermediate risk is 14 months and poor risk is 5 months [8].

2. TREATMENT-NAÏVE PATIENTS

a) Treatment-naïve patients with favourable or intermediate prognosis

Sunitinib is a multi-kinase inhibitor (TKI) that acts mainly on the VEGF receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR). In a Phase III trial of sunitinib versus interferon alpha (IFN- α) in untreated patients with mRCC, sunitinib demonstrated significant improvements in objective response rate (ORR; independent review, 31% vs 6%; $p < 0.000001$), median progression-free survival (PFS; 11 mo vs 5 mo; $p < 0.001$) and overall survival (OS; 26.4 mo vs 21.8 mo; hazard ratio [HR], 0.821; $p = 0.051$) [9-10]. These data have led to sunitinib being recommended as a first-line therapy for patients with mRCC [11] (figure 1).

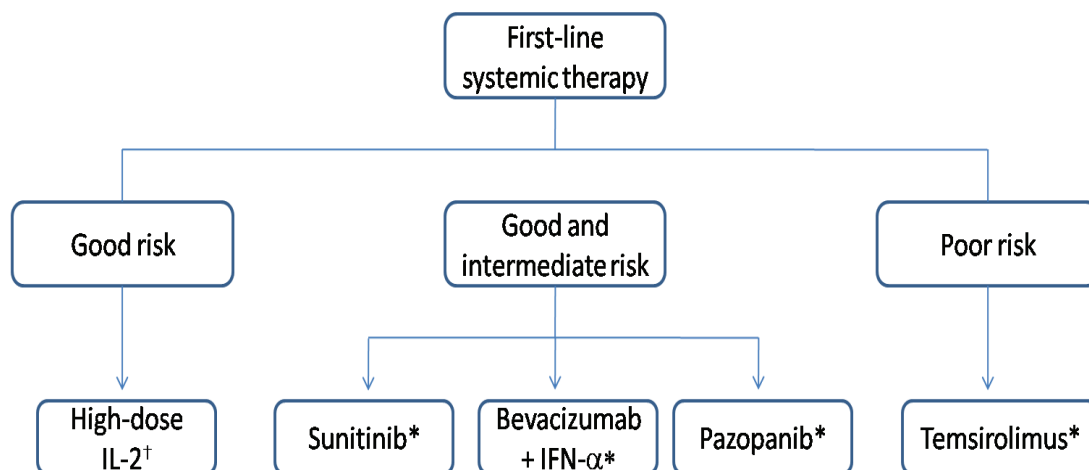
Bevacizumab, a monoclonal antibody targeting the VEGF ligand directly, in combination with IFN- α , has shown efficacy in two Phase III trials in patients with previously untreated mRCC [12-15]. In the first of these studies, median PFS was 10.4 mo for bevacizumab plus IFN- α compared with 5.5 mo for IFN- α alone ($p < 0.0001$) [12]. No significant difference in overall survival was observed (23.3 mo vs 21.3 mo; $p = 0.1291$) [16]. Consistent results were seen in the second study, performed by the Cancer and Leukemia Group B, with median PFS of 8.4 mo and 4.9 mo, respectively ($p < 0.0001$) [13]. Again, no significant difference in OS was observed (18.3 mo vs 17.4 mo; $p = 0.069$) [17]. The PFS benefits seen in these trials are similar to those obtained with sunitinib in therapy-naïve patients with advanced

RCC [9], and supports bevacizumab plus IFN- α as another acceptable and effective therapy in the first-line setting [11] (figure 1).

Pazopanib has a similar broad spectrum of kinase inhibition, including VEGFR1-3, PDGFR-A and -B, and c-Kit [18]. The results of a phase 3 trial versus placebo in patients who either received no prior therapy or who failed on prior therapy with cytokines or bevacizumab has recently been reported [19]. Four hundred thirty-five therapy-naïve and cytokine-pretreated mRCC patients were randomized to oral pazopanib or placebo (randomisation 2:1 for pazopanib), with PFS as the primary endpoint. In both treatment-naïve and pretreated patients there was a significant benefit in PFS. The median PFS for pazopanib as compared to placebo was 9.2 vs 4.2 months and in treatment-naïve patients, 11.1 vs 2.8 months, respectively ($p < 0.0000001$). Data are immature with regards to OS. This data has led to pazopanib receiving FDA approval in the US (figure 1).

b) Treatment-naïve patients with poor prognosis

Temsirolimus is an intravenously administered inhibitor of mTOR. A randomized, Phase III trial compared monotherapy with temsirolimus versus IFN- α versus temsirolimus plus IFN- α as first-line treatment in patients with mRCC and poor prognosis [20]. Patients were required to have at least three of six predictors of a poor prognosis and survival according to a prognostic factor scheme modified from the MSKCC model. Patients who received temsirolimus alone, compared with those who



* Grade A recommendation, †grade B recommendation.

Figure 1. Treatment schematic for patients with metastatic clear-cell renal cell carcinoma in the first-line setting

received IFN- α alone or the combination had greater PFS (5.5 \pm 3.1 \pm 4.7 mo, respectively), OS (10.9 \pm 7.3 \pm 8.4 mo) and ORR (8.6% \pm 4.8% \pm 8.1%). The results of this trial justify mTOR as a target for renal cancer treatment and recent European guidelines recommend that temsirolimus be considered as first-line treatment in poor-risk patients [11] (**figure 1**).

3. CYTOKINE-REFRACTORY PATIENTS

Sorafenib is a small-molecule multikinase inhibitor of VEGFR and related receptors, and also inhibits the intracellular signalling of Raf kinase. In a placebo-controlled, Phase III trial involving patients with mRCC who had failed previous cytokine therapy, a PFS advantage for sorafenib of 5.5 mo versus 2.8 mo ($p < 0.001$) was observed [21–22]. Partial responses were reported as the best response in 10% of patients receiving sorafenib and in 2% of placebo recipients ($p < 0.001$). Disease control rate was higher for sorafenib than placebo (62% \pm 37%; $p < 0.001$) [21]. An improved OS with sorafenib was observed after censoring placebo patients who had crossed over to sorafenib (17.8 mo \pm 14.3 mo; $p = 0.0287$) [22]. Based on the results of this trial, sorafenib is recommended as a second-line agent in cytokine-refractory patients [11] (**figure 2**).

The efficacy of sunitinib in a total of 169 patients with mRCC who progressed on prior cytokine therapy was demonstrated in two Phase II trials [23–24]. Across the two trials, partial responses were reported in 34–40% of patients and a median PFS of 8.3–8.7 mo was observed.

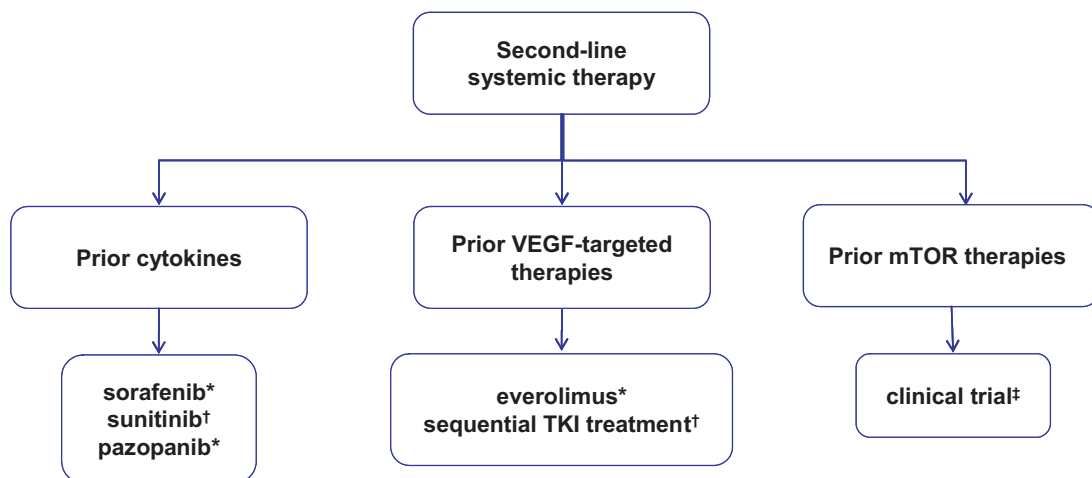
Taken together, these data indicate that either sorafenib or sunitinib may be a valid second-line

treatment options for patients who have failed prior cytokine-based therapies.

Pazopanib, in the recently reported phase III trial comparing its efficacy over placebo in naïve and cytokine refractory patients also demonstrated a PFS advantage in the latest group (median PFS 7.4 \pm 4.2 months, p value < 0.001) [19]. This has led to pazopanib's approval by the FDA in the second line setting after cytokine failure (**figure 2**) and is under evaluation by the EMEA.

4. VEGF-TARGETED THERAPY-REFRACTORY PATIENTS AND SEQUENTIAL THERAPY CONCEPT.

Substantial clinical benefit has been obtained from retrospective or phase II trials by novel TKIs, including sunitinib, sorafenib and axitinib, in patients with mRCC failing a VEGF-targeted therapy [25–29]. The RECORD-1 trial has explored the possibility to switch to an agent with a different mechanism of action and molecular target, i.e. an mTOR inhibitor such as everolimus [30]. In this Phase III trial, patients receiving everolimus (10 mg once daily $n = 272$) had significantly prolonged PFS versus those on placebo ($n = 138$; 4.0 mo \pm 1.9 mo; HR, 0.30; $p < 0.0001$). The end of the double-blind analysis from this trial indicated a further improvement in PFS with everolimus treatment (4.90 mo [$n = 277$] versus 1.87 mo [$n = 139$]; HR, 0.33; $p < 0.001$). The PFS benefit following treatment with everolimus was maintained across patients with favorable ($n = 120$), intermediate ($n = 235$) or poor ($n = 61$) MSKCC prognosis. At the end of the double-blind analysis, median OS was 14.78 mo in the everolimus group



* grade A recommendation; † grade B recommendation; ‡ grade C recommendation

Figure 2. Treatment schematic for patients with metastatic clear-cell renal cell carcinoma in the second-line setting

and 14.39 mo in the placebo group. Crossover from placebo to the active treatment arm was allowed after disease progression, potentially confounding OS; 81% of placebo recipients who progressed crossed over to everolimus treatment.

Two other randomised phase III trials are currently recruiting to look for the position of temsirolimus and axitinib as second line options. The AXIS trial is testing axitinib versus sorafenib in patients failing any of the first line regimens such as sunitinib, bevacizumab+interferon, temsirolimus or cytokines. The second trial is a prospective randomised phase III trial of temsirolimus versus sorafenib as second line therapy in patients who have failed first line sunitinib option. In both trials, PFS is the primary endpoint.

Other trials are ongoing to determine the optimal TKIs/TKIs or TKIs/mTOR inhibitors drug sequence. Based on several retrospective reports showing that the sequence of sorafenib given prior to sunitinib may be superior when compared to the reverse sequence, an ongoing phase 3 trial (SWITCH trial) has been designed to define the best sequence of TKIs. Another trial is the RECORD-3 study. This is an open-label, multicenter phase II study to compare first-line everolimus followed by second-line sunitinib versus the opposite sequence (first-line sunitinib followed by second-line everolimus) in the treatment of patients with mRCC (NCT00903175).

5. DRUG COMBINATION

The concept of anti-angiogenic drug combination is to enhance drug monotherapy efficacy by vertical or horizontal blockade. The inhibition of several steps of the same pathway (HIF-VEGFR-VEGFR) is a "vertical" blockade while targeting in parallel 2 separate pathways with different functions (PDGFR, VEGFR, EGFR) is considered as an horizontal "blockade" [31].

The combination of bevacizumab and sunitinib has been explored in a phase I study [32]. Nineteen patients with mRCC received escalating doses of sunitinib from 25 to 50 mg daily with fixed-dose bevacizumab (10 mg/kg IV). Dose-limiting toxicity (DLT) was grade 4 haemorrhage in one patient in each of the higher doses and one fatal myocardial infarction at the highest dose. All levels of treatment induced a 37% PR. The toxicity seen with these two agents precluded further development of the combination.

The combination of bevacizumab and sorafenib has been explored in a phase I trial [33]. Sixteen patients were included for a dose-escalation. Grade 3 proteinuria and uncontrolled grade 3 hypertension were the DLTs at the highest level, corresponding to the maximum tolerated dose (MTD). The recommended dose was sorafenib at 200 mg twice

daily (BID) and bevacizumab at 5mg/kg. Interesting synergistic antitumor activity was observed with this combination.

Other phase I trials have explored the combination of TKIs inhibitors with IFN. In these trials, patients received sunitinib or sorafenib and IFN- α with DLTs that included fatigue and myelosuppression. Only inferior dosages of both sunitinib or sorafenib and IFN- α , compared to optimal dosages in monotherapy, were manageable. Phase II studies have evaluated the combination of sorafenib and IFN- α at standard or low dose without clear superior benefit for the combination [34-37].

Temsirolimus and bevacizumab were combined in a phase I study during which the recommended weekly dose of temsirolimus 25 mg/kg IV and bevacizumab at a dose of 10 mg/kg /2 weeks were utilized. DLTs encountered were grade 3 stomatitis and hypertriglyceridemia. Among 12 evaluable patients, 8 PR were reported. Based on the preliminary results reported, a randomised phase III trial (INTORACT) is ongoing comparing temsirolimus/bevacizumab with bevacizumab/IFN.

The temsirolimus and sorafenib combination has also been evaluated [38]. Patients were treated with escalating continuous oral doses of sorafenib (200 and 400 mg BID) and weekly IV temsirolimus (15 mg, 25 mg). Thirty three evaluable patients showed DLTs including grade 3 hand-foot syndrome, mucositis, rash, thrombocytopenia, neutropenia and creatinine elevation. The full recommended dose of both drugs appeared unachievable mainly due to mucositis.

Bevacizumab in combination with the oral mTor inhibitor everolimus is a promising combination in first and second line settings [39]. Presently, a randomised phase II trial is ongoing comparing bevacizumab/everolimus with bevacizumab/IFN (RECORD-2).

Other randomised phase II or III trials are being conducted. The BeST trial is a 4 arms randomised ECOG phase 2 trial (E2804) evaluating front line therapy with bevacizumab & temsirolimus and bevacizumab & sorafenib and bevacizumab & temsirolimus and sorafenib. The TORAVA trial is a phase II trial comparing bevacizumab plus interferon & bevacizumab plus temsirolimus & sunitinib. Enrolment is closed and results should be available shortly [31]. The current opinion of most investigators regarding combination therapy is that until it has clearly shown to be superior to monotherapy, it should not be used outside the context of clinical trials. Results of ongoing trials are eagerly awaited.

6. THE ROLE FOR NEPHRECTOMY IN THE ERA OF TARGETED THERAPIES

Two randomised studies have demonstrated that

nephrectomy is associated with a survival advantage in selected IFN treated mRCC patients [40-41]. Based on these results, primary tumour removal is currently part of the standard of care in mRCC. However, no equivalent evidence has been obtained with anti-angiogenic drugs so far even though it remains reasonable to remove large tumours that are likely to cause local complications under treatment. By contrast to cytokine based therapy, TKIs are indeed able to cause significant responses within the primary kidney tumour [42]. Therefore, TKIs could be used in the neo-adjuvant setting for selecting those good and intermediate risk patients who may benefit from nephrectomy [43]. In several phase II trials presurgical sunitinib or bevacizumab has demonstrated sufficient safety and efficacy [44-46].

A subgroup analysis from the phase III trial comparing temsirolimus with IFN in poor risk patients demonstrated similar survival benefit for temsirolimus regardless of patient nephrectomy status, thus suggesting that nephrectomy may have a limited role in poor risk patients [47].

Two phase III randomised studies, addressing respectively the questions of the role of upfront therapy and of the timing of nephrectomy, are currently ongoing in Europe [48]. The CARMENA trial is a phase III randomised study comparing nephrectomy plus sunitinib vs sunitinib without nephrectomy in first-line metastatic RCC. Primary end point is overall survival. The EORTC trial (SURTIME trial) is a randomised phase III trial comparing sunitinib followed by nephrectomy in case of non-progressive metastases followed by sunitinib vs nephrectomy followed by sunitinib in patients with synchronous metastatic renal cell carcinoma. The primary endpoint is progression free survival.

7. THE ROLE OF METASTASECTOMY.

The 5 years survival rate for patients undergoing RCC metastases resection ranges from 35 to 60% [49]. Interval from RCC diagnosis to occurrence of metastases superior to 1 year, a unique metastatic site and age inferior to 60 years have been identified as favourable survival predictive factors following RCC metastases resection [50]. In case of pulmonary resection, delay from RCC diagnosis to metastases occurrence, complete resection, number of nodules to remove, metastatic nodule size appear as major prognostic factors [51-54]. The 5 years survival rate seems to be superior in case of pulmonary resection (54%) than in case of brain resection (18%) [50]. Pancreatic metastases are likely to occur late in the natural history of the metastatic disease and seem to have a good prognosis when a surgical resection is feasible [55]. Due to the emergence of effective targeted therapies, the concept of tumour metastasectomy needs to be revisited for potentially rendering patients free of disease following combined surgical and medical treatments [49-56].

IV. PANEL CONSENSUS RECOMMENDATIONS.

1. Sunitinib monotherapy and bevacizumab in combination with IFN- α may be considered first-line treatment options in patients with metastatic or unresectable clear-cell RCC and favourable or intermediate prognosis according to MSKCC criteria (Grade A).
2. In the first line setting, temsirolimus is recommended in patients with poor prognostic features according to modified MSKCC criteria (Grade A).
3. In the second-line setting, sorafenib treatment is recommended for patients with mRCC refractory to cytokines (Grade A).
4. In the second-line setting, everolimus treatment is recommended for patients refractory to VEGF-targeted therapy (Grade A).
5. Pazopanib is a new therapeutic option in first line setting or in cytokine refractory patients (Grade A).
6. Cytokines, including high-dose interleukin-2 remain an option for first-line treatment of highly-selected patients with metastatic clear cell RCC and good prognosis (Grade B).
7. Sunitinib is a possible alternative to temsirolimus as first-line treatment in patients with poor prognosis and also as an alternative to sorafenib as a second-line treatment after cytokines (Grade B).
8. For patients refractory to mTOR inhibitors, enrolment in clinical trials is advised (Grade C).
9. Anti-angiogenic drug combinations are still investigational (Grade B).
10. The sequential therapy concept is validated by phase II and III trials. Further trials are needed to determine the optimal intra or inter drug class sequencing (Grade B).
11. Based on previous randomised studies with IFN, upfront nephrectomy is advised in appropriately selected patients. However, further phase III clinical trials should clarify its exact role in the current therapeutic era. Nephrectomy is not likely to be useful in poor risk patients according to MSKCC criteria (Grade B).
12. Surgical Resection of a unique metastasis should be considered as a valuable therapeutic option, particularly in cases of delay between RCC diagnosis and occurrence of metastasis exceeding 1 year, young age or favourable prognostic features and when a complete resection is expected. The concept of tumour metastases resection should be revisited in the era of targeted therapy (Grade C).

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